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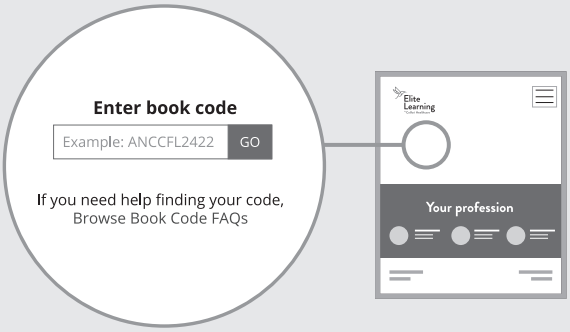

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Pharmacy Law	RPFL03PL
The Role of the Pharmacist in the Opioid Crisis	RPFL05PO

Chapter 1: Patient Safety and Medication Errors in Florida (Mandatory)

2 Contact Hours

By: Bradley Gillespie, PharmD

Author Disclosure: Bradley Gillespie and Colibri Healthcare, LLC do not have any actual or potential conflicts of interest in relation to this lesson.

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Learning objectives

At the conclusion of this knowledge-based learning activity, the pharmacist will be able to:

- Describe the significance of the Institute of Medicine's 1999 and 2006 report on medication errors.
- Define and distinguish between the following terms: safe medication, drug safety, quality issues, medication errors and adverse drug events.
- List each of the governing bodies involved in medication safety (FDA, AHRQ, IOM, USP, NCC, ISMP, JCAHO).
- Identify the types of medication errors made by pharmacists.
- Discuss additional reasons that pharmacists may cause a medication error, as defined by the Food and Drug Administration.
- Identify the ways a patient may be responsible for initiating a medication error.
- Discuss the format for reporting a medication error.
- Discuss Florida's law for the Pharmacy Continuous Improvement Program.
- Identify ways to promote medication safety for patients.
- Identify the six medication "rights" to improve patient safety.
- Discuss recommendations to improve patient safety during the distribution phase of drug administration.
- Identify the consumer's role in improving medication safety.

Pre-assessment questions

Prior to beginning work on this activity, test your baseline knowledge by answering the following questions. These questions may be repeated in the final examination.

1. Which of the following is <u>not</u> a component of a safe medication system?
   a. Administration of the drug.
   b. Preparation and dispensation of the drug.
   c. Selecting the generic equivalent that provides the best profit margin.
   d. Selection and procurement of the drug by a pharmacy.
2. Many Internet pharmacies try to alleviate patient anxiety by noting that they are ordering their prescriptions under the concept of "responsible self-treatment." Which of the following are components of responsible self-treatment?
   a. There are no medications with guaranteed efficacy.
   b. Most medications are safe.
   c. The Internet pharmacy takes full responsibility for the patient's safety.
   d. All medications act independent of each other.
3. FDA has determined that it is always safe to purchase medications from Internet pharmacies.
   a. True.
   b. False.

Introduction

Over the past decade, medication safety has been a big concern for pharmacists who dispense or administer medications to patients. The Institute of Medicine (IOM) states that even though medication errors can occur anywhere within a safe medication system, it occurs more frequently in the prescription and administration processes.[1] Pharmacists need to be especially concerned with the prevention of errors during the process of preparing and dispensing medications.

In 1999, the public learned about medication errors when the Institute of Medicine (IOM) released a report, "To Err is Human: Building a Safer Health System." The IOM report disclosed that an estimated 44,000 to 98,000 deaths result from medical errors in hospitals alone, with 7,000 of the deaths related to medications.[2] The report was a revelation to patients, families and the entire health care team.

As pharmacists, it is imperative to understand the legalities, responsibilities and accountability that we have to patients while participating in any component of the medication administration process.

In 2004, the Food and Drug Administration (FDA) reported alarming data provided by the Slone Epidemiology Center at Boston University, showing that in a given week, half of U.S. adults will use prescription drugs, and 10 percent will take at least five different medications.[3]

In 2006, the IOM reiterated the data, as it estimated that in any given week, four out of every five adults will use a prescription medicine, over-the-counter (OTC) drug, or dietary supplement, and nearly one-third of adults will ingest five or more different medications.[4]

In 2001, Ernst and Grizzle estimated that the total cost of drug-related morbidity and mortality in the ambulatory care setting was more than $177 billion, which is greater than the cost of the medications themselves.[5]

To avoid even unintentional harm to patients, health care professionals must understand and abide by the expectations bestowed upon them. Patients and their families put their trust in health care professionals each time they enter a health care facility. It is our duty as pharmacists to serve and protect each patient by appreciating the power of each drug before dispensing any medication to a patient.

Definitions related to the safety of medications

The FDA defines "safe" medication as one whose benefits outweigh the risks for patients.[27] The IOM uses the terms "drug safety" and "quality issues" in discussion of the safe, effective, appropriate and efficient use of medications.[6] There are five components in a safe medication system:

1. Selection and procurement of the drug by a pharmacy.
2. Prescription and selection of the drug for the patient.
3. Preparation and dispensation of the drug.
4. Administration of the drug.
5. Monitoring of the patient for its effect.[30]

Although all of these items are not always under the watchful purview of the pharmacist, he or she should be at least mindful, if not fully responsible, for all of these critical points.

A medication error is defined by the National Coordinating Council (NCC) as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient or consumer."[7]

In 1996, the NCC classified a medication error based upon the severity of the outcome to ensure that all health care professionals use the same terminology and to track errors in a consistent, systematic manner.[8] In July 2006, the National Academies of the IOM released a report that claimed 1.5 million people are harmed annually by medication errors, which cost more than $3.5 billion a year.[9] This figure alone should be adequate to get the attention of all practicing pharmacists.

Further, in 2006, a study showed that the most common medical errors are related to medications.[10]

Adverse drug events are defined as "any response to a drug which is noxious or unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease."[11] According to the Agency for Healthcare Research and Quality (AHRQ), more than 770,000 people are injured or die each year in hospitals from adverse drug events, which may cost up to $5.6 million each year per hospital, depending on hospital size.[12]

Although the data is alarming, this estimate did not include the effect of adverse drug events on the length of the admission, malpractice and litigation costs, or the costs of injuries to patients. The AHRQ estimates that the cost to U.S. hospitals to treat patients who suffer adverse drug events during hospitalization is between $1.56 and $5.6 billion annually.[35]

According to the IOM, although adverse drug events are rising and considered preventable, it is difficult to obtain an accurate measurement of how often preventable adverse drug events occur in the various phases of the drug use process. The IOM alludes to studies over the past few years estimating that anywhere from 380,000 to 800,000 preventable adverse drug events occur annually – however, the committees believe that these are underestimates. According to the IOM committee, although the data varies depending on the study, it is estimated that 1.5 million preventable adverse drug events occur in the U.S. annually.[13]

Governing bodies

To have a better understanding of medication safety, it is important to understand that there are many agencies and organizations eager to promote the safety of medications for patients and health care professionals alike. Each is geared toward monitoring the efficacy of every medication on the market, and providing education to the public and health care professionals. Below are a few of the agencies and organizations that monitor adverse drug events and medication errors every year.

HHS: The U.S. Department of Health and Human Services (HHS) is the government's principal agency for protecting the health of all Americans and providing essential human services, especially for those who are least able to help themselves. HHS encompasses more than 300 programs related to the health of Americans, including safe monitoring and administration of medications.

For fiscal year 2014, the HHS budget is approximately $967.3 billion.[14] There are two U.S. public health agencies under the HHS responsible for the efficacy encompassing medications, the Food and Drug Administration and the Agency for Healthcare Research and Quality.[15]

FDA: The Food and Drug Administration (FDA) is well known to the public and health care professionals. The FDA began as a single agency with a single chemist in 1862. In 1906, the Federal Food and Drug act was passed, but the FDA did not get its name until July 1930.[16] The FDA's mission is to protect public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, the nation's food supply, cosmetics and products that emit radiation.[17]

While FDA regulates and approves all medications, it does not usually conduct the research supporting these approvals. Within the FDA, there are numerous groups responsible for ensuring patient safety, public knowledge and the prevention of medication errors. FDA has collaborated with other agencies to establish a standard framework to electronically share important data about medications to promote efficiency and safety.[18] FDA has a subsidiary component, called MedWatch, that is responsible for safety information and adverse event reporting.[19]

AHRQ: The Agency for Healthcare Research and Quality (AHRQ) was established in 1989 as the Agency for Health Care Policy and Research. Reauthorizing legislation passed in November 1999 established AHRQ as the lead federal agency on health care quality research. AHRQ, part of the U.S. Department of Health and Human Services, is the lead agency charged with supporting research designed to improve the quality of health care, reduce its cost, and broaden access to essential services. AHRQ has completed a vast amount of research on medication errors, medication safety and the effect on patients.[20]

The National Academy of Sciences is an adviser on scientific and technological matters. It was chartered by the U.S. government under the auspices of President Abraham Lincoln in 1863. In 1970, the Institutes of Medicine (IOM) was founded as an independent, nonprofit organization that provides unbiased and highly authoritative information needed to guide

government decision makers and the public. Although the IOM is independent and works outside of the government, it serves as the health arm of the National Academy of Sciences.[21] The unique component of the IOM is that researchers and scientists are unpaid volunteer experts, dedicated to promoting safe medication practices.

IOM: The Institute of Medicine (IOM) encompasses experts and scientists tasked with improving the lives of millions of people around the world using evidenced-based practice.[22] The IOM is mandated by Congress, through the Medicare Modernization Act of 2003 (Section 107 (c)), to "carry out a comprehensive study of drug safety and quality issues in order to provide a blueprint for system-wide change."[23]

One of the committees involved in promoting medication safety within the IOM is formed from within the Center for Drug Evaluation and Research (CDER) at FDA. CDER's goal is to review the drug information, safety surveillances and key aspects of the contributions of the pharmaceutical industry, academic research, Congress and patients using medications.[24]

For-profit organizations

USP: The United States Pharmacopeia (USP) is the official public standards-setting authority for all prescription and over-the-counter medicines, dietary supplements and other health care products manufactured and sold in the United States. USP sets standards for the quality of these products, and works with health care providers to achieve those standards. The USP standards are also recognized and used in more than 130 countries. It has helped ensure the manufacture of high quality pharmaceuticals, as well as reliable pharmaceutical care, for people throughout the world, for more than 185 years.[25]

NCC: In 1995, the National Coordinating Council (NCC) was established to promote the safe use of medications. The mission of the National Coordinating Council for Medication Error Reporting and Prevention (NCC-MERP) is to maximize the safe use of medications and to increase awareness of medication errors through open communication, increased reporting, and promotion of medication error prevention strategies.[26] The NCC-MERP helps to heighten awareness of medication reports within the health care system and provides education on medication errors for consumers and health care professionals. Further to that, NCC-MERP develops comprehensive literature reviews, describing the safe use of medications. Its goal is to protect patients by not allowing any patient to be harmed by a medication error.[27]

Nonprofit organizations promoting patient safety

ISMP: The Institute for Safe Medication Practices (ISMP) began in 1975 as a nonprofit organization that receives no advertising revenue and is devoted entirely to medication error prevention and safe medication use.[28] The ISMP took over management of the United States Pharmacopeia-developed Medication Errors Reporting Program (USP-MERP) in late 2008, re-branding it as ISMP MERP.

ISMP MERP is designed for reporting the cause of medication errors and provides recommendations for preventing future errors, always identifying the erroneously used medication. In addition, the ISMP reports to the appropriate regulatory agency and the manufacturer of the company. To assess whether any medication has been incorrectly listed anywhere, the Institute for Safe Medication Practices continuously updates its website, noting any incorrect data published in textbooks and publications.[29]

JCAHO: Joint Commission on Accreditation of Healthcare (JCAHO) is a nonprofit organization that has been affiliated with monitoring patients in some capacity since 1910. In 1965, Congress passed the Social Security amendment that incorporated a provision in which each hospital needs to be JCAHO-accredited to receive reimbursement for patient care from Medicare or Medicaid.[30] The goal of JCAHO is to improve the safety and quality of care provided to the public through the provision of health care accreditation and related services that support performance improvement in health care organizations.

Background

As pharmacists, we enter the profession so that we may care for others, and to ensure that no harm comes as a result of this care. Although one's intentions may be good while caring for a patient, medication errors do occur on a daily basis, often at the expense of the patient.

Regardless of the circumstances, while caring for another, it is important to remember: "I am here to care for this patient and family; they have put their trust in me." We must remember to treat each patient as we would want our loved ones to be cared for while in the hands and at the mercy of the health care system.

Throughout our health care system, with today's economic realities, professionals encounter shortages in their departments. Although it may induce more stress in the workplace, that should not affect safe medication practices and pharmaceutical care.

To bring change to the system, it is imperative to recognize the components that contribute to medication errors. According to McLeod (2007), the Joint Commission Journal on Quality and Patient Safety has said that nearly 5 percent of errors reported to the national database for medication errors from 2004 to 2006 involved medication abbreviations, and the majority (81 percent) occurred during the prescribing phase.[31]

Based upon the study of nearly 30,000 abbreviation-related medication errors, JCAHO in 2005 initiated the "Official Do Not Use List" that was implemented in the hospitals nationwide (See Table 1).[32] Of the common abbreviations used by many experienced health care professionals, "QD" for "once daily" was associated with more errors than any other abbreviation, followed by "U" for units (13.1 percent), "cc" for milliliter (12.6 percent) and "MSO4" or "MS" for morphine sulfate (9.7 percent).[28] The "Official Do Not Use List" is being used by health care professionals nationwide, and it was also incorporated into JCAHO's patient safety goals.[32]

The ISMP recommends that health care professionals do not stop at the minimum guidelines of JCAHO standards on abbreviations to avoid preventing medication errors. Since 2006, the ISMP has offered a more comprehensive list that can be accessed on the Internet.[33]

Florida Law and the Continuous Quality Improvement Program

The Institute of Medicine's 1999 groundbreaking report on medical errors has led to some state boards, including Florida, to examine ways to reduce these errors. Florida Law states in Sec. 64B16-27.300 of the Florida Standards for Practice for pharmacists that each pharmacy shall establish a Continuous Quality Improvement (CQI) Program and that the program shall be described in the pharmacy's policy and procedure manual . The Continuous Quality Improvement Program is a system of standards and procedures to document quality-related events and improve patient care. A "Quality-Related Event" means the inappropriate dispensing or administration of a prescribed medication including :

A. A variation from the prescriber's prescription order, including, but not limited to:
   - Incorrect drug;
   - Incorrect drug strength;
   - Incorrect dosage form;
   - Incorrect patient; or
   - Inadequate or incorrect packaging, labeling, or directions.

B. A failure to identify and manage:
   - Over-utilization or under-utilization;
   - Therapeutic duplication;
   - Drug-disease contraindications;
   - Drug-drug interactions;
   - Incorrect drug dosage or duration of drug treatment;
   - Drug-allergy interactions; or
   - Clinical abuse/misuse.

At a minimum the pharmacy's CQI Program shall contain provisions for a Continuous Quality Improvement Committee, provisions to ensure that the committee conducts a review of the Quality Related Events at least every three months, a planned process to record, measure, assess, and improve the quality of patient care and the procedure for reviwing Quality Related Events.

Each Quality-Related Event that occurs, or is alleged to have occurred, as the result of activities in a pharmacy, shall be documented in a written record or computer database created solely for that purpose. Documentation of a Quality-Related Event shall include a description of the event and Pharmacists shall maintain the records at least until the event has been considered by the committee and incorporated in the summary required by Florida law. Records maintained as a component of a pharmacy Continuous Quality Improvement Program are confidential.

Types of medication errors involving health care professionals

According to FDA, medication errors contribute to at least one death every day, and injure approximately 1.3 million people annually in the United States. Between 1993 and 1998, the FDA completed a study in which it found that the most common medication errors were the following:

- Administration of an improper dose of medicine, accounting for 41 percent of fatal medication errors.
- Administration of the wrong drug, accounting for 16 percent of fatal medication errors.
- Administration of medicine using the wrong route of administration, accounting for 16 percent of fatal medication errors.

Almost half of the fatal medication errors occurred in people over the age of 60. Older people may be at greatest risk for medication errors because they often take multiple prescription medications.[34] With the pharmacist's combination of training and experience, we are often in an ideal position to identify and correct these types of errors and have a favorable impact on overall patient well-being.

The FDA has stated that a medication error can occur during any of the following components of the drug-use process:[35]

- Prescribing.
- Repackaging.
- Dispensing.
- Administering.
- Monitoring the patient for side effects and adverse drug events.

Additionally, FDA has provided other common causes of medication errors:[35]

- Poor communication between doctors, nurse practitioners, nurses or pharmacists.
- Ambiguities in the product name, directions for use, medical abbreviations or the legibility of the writing.
- Poor procedures and techniques.
- Patient misuse because of poor understanding of the directions for use of the product.

Again, pharmacists will often find themselves in a position to rectify many of these trouble points in the medication process.

In 2006, new data confirmed the FDA's study of 1990, stating that the most common medication errors included nurses administering the wrong medications or wrong dose in an intravenous drip, physicians prescribing drugs that could cause a dangerous interaction with patient's other medications, and pharmacists dispensing 100-milligram tablets when 50-milligram tablets were prescribed.[36] Through training and intense attention to detail, pharmacists can work to eliminate errors directly under their purview. And they are also well positioned to collaborate with nurses and prescribers to help reduce the incidence of most errors in the prescription or administration of medications.

Types of medication errors initiated by a patient

Although health care professionals have made many medication errors over the years, an error can also be committed intentionally or unintentionally by the patient. The first potential problem as noted by the IOM in 2006 is that 50 percent of patients do not take their medications as prescribed.[10] As pharmacists, we have to change the way that we communicate with our patients, sharing our education and knowledge in the hope that they will take their medications as prescribed, safely.

Patients may perceive that a medication is simply a "quick fix" to a problem; as pharmacists, we need to teach them about each medication's purpose, potential side effects, drug-drug interactions, drug-food interactions and safety concerns. Patients should also be reminded that before using any OTC medication or herbal product, they should check with their doctor or health care practitioner because those products may interact with current medications and health conditions in the same manner as other medications.

Another potential problem is drug abuse. In 1999, the National Institute on Drug Abuse (NIDA) reported that 4 million Americans 12 years or older had used a prescription medication for non-medical reasons.[37] Therefore, it is incumbent on the pharmacist to be aware of this fact and assess each patient who may abuse a prescriptive or non-prescriptive medication provided to them.

A third potential medication error initiated by a patient is purchasing a medication, with or without a prescription, on the Internet. A patient may have a preconceived notion that he or she wants or needs to be on a certain medication after reading or hearing an advertisement from a pharmaceutical company. If the patient's primary care physician refuses to write a prescription, a patient often can purchase the medication online without a prescription. In other cases, Internet pharmacies are abused by patients who have tendencies towards self-medication, not believing that they need the guidance of a qualified prescriber.

Some websites and companies attempt to alleviate patients' concerns about the practice by noting that they are ordering under the concept of "responsible self-treatment":

- The term "self-treatment" means that the patient takes responsibility for the results obtained by controlling their own access to medication. Responsible self-treatment assumes that the patient owns the information on an accepted preparation, and realizes the following:
  - There is no such thing as an absolutely safe medicine.
  - There are no medicines with guaranteed efficacy.

- Any medicines accepted simultaneously can interact positively or negatively with each other.

According to the World Health Organization (WHO), responsible self-medication is a practice where patients can treat their conditions and ailments using medicines that are approved and available in their region without a prescription. Further, these medications must be proven to be safe and effective. This WHO definition does not seem to align with the message inferred by Internet pharmacies promoting this practice.[38]

It is unfortunate that there are unprofessional, misleading and illegal sites available to encourage and promote the purchase of more than 1,800 medications, including high-risk medications such as Viagra, Vicodin and Xanax. These sites sometimes even provide a "consultation" with a physician for the patient to obtain a prescription for a narcotic or other dangerous medications.

Another reason why patients may consider purchasing a medication online is concern about their rising medication costs. It is estimated that 4 percent of Americans have purchased their medications online.[39] Because other countries do not regulate their medications to the standards of the FDA, the agency conducted a research investigation into the importation of medications from various countries, focusing on the safety of the medication and the potential efficacy of these imported medications for patients. The FDA investigation discovered the following:

> Of the 2,069 drug orders examined, 88 percent appeared to be prescription medications available in the United States. The remaining 12 percent were dietary supplements, had illegible or incomprehensible labeling, or were not available in the U.S. "The most surprising finding was the motivation of patients to use Internet pharmacies. FDA investigators believed that many people were not buying the drugs to save money, but to bypass the need for a prescription."[40]

FDA recommends that patients can purchase medications safely online if they are purchased through a pharmacy physically located in the United States. It also said the following medications should never be purchased online or from a foreign source because safety controls are often bypassed, placing patients at risk for adverse drug events:

- **Accutane (isotretinoin)** – indicated for the treatment of severe, recalcitrant nodular acne.
- **Actiq (fentanyl citrate)** – indicated for the management of severe cancer pain in patients who are tolerant to opioid therapy.
- **Clozaril (clozapine)** – indicated for the management of severe schizophrenia in patients who fail to respond to standard drug treatments for schizophrenia.
- **Humatrope (somatropin for injection)** – indicated for the treatment of non-growth hormone-deficient short stature.
- **Lotronex (alosetron hydrochloride)** – indicated for the treatment of severe irritable bowel syndrome in women.
- **Mifeprex (mifepristone or RU-486)** – indicated for the medical termination of early intrauterine pregnancy.
- **Plenaxis (abarelix for injectable suspension)** – indicated for the treatment of advanced symptomatic prostate cancer in men who are not able to receive other types of treatment.
- **Thalomid (thalidomide)** – indicated for the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum.
- **Tikosyn (dofetilide)** – indicated for the maintenance of normal sinus rhythm in patients with certain cardiac arrhythmia.
- **Tracleer (bosentan)** – indicated for the treatment of severe pulmonary arterial hypertension.
- **Trovan (trovafloxacin mesylate or alatrofloxacin mesylate injection)** – an antibiotic administered at in-patient health care settings for the treatment of severe, life-threatening infections.
- **Xyrem (sodium oxybate)** – indicated for the treatment of cataplexy in patients with narcolepsy.[41]

Reporting a medication error

If a medication error should occur in any format, as a registered pharmacist, you have a professional, ethical and legal obligation to report it to the appropriate authorities. Within the United States, the Medication Error Reporting program (MER) and the FDA work in conjunction to monitor the efficacy of each medication to prevent future medication errors. Since March 13, 2003, the FDA has required that all actual and potential medication errors must be submitted to the agency within 15 calendar days.[42] Additionally, FDA reviews medication error reports that come from drug manufacturers using the MedWatch reporting system and ISMP MERP.

The following organizations are obligated to track medication errors:

- FDA – Accepts reports from consumers, health professionals and drug companies about products regulated by FDA, including drugs and medical devices, through MedWatch, the FDA's safety information and adverse event reporting program.
- Institute for Safe Medication Practices MERP – Accepts reports from consumers and health professionals on medications and publishes Safe Medicine, a consumer newsletter on medication errors.[43]
- Quantros – MedMARX is an anonymous medication error reporting program used by hospitals that was developed by USP but managed by Quantros since late 2008.[44]

According to the ISMP MERP program,[43] all health care professionals should report actual or potential medication errors that occur due to any of the following reasons:

- Errors in the prescribing, transcribing, dispensing, administering and monitoring of medications and vaccines.
- Wrong drug, wrong strength, or wrong dose.
- Wrong patient.
- Confusion over look-alike/sound-alike drugs or similar packaging.
- Wrong route of administration.
- Calculation or preparation errors.
- Misuse of medical equipment.

It should be noted that a potential medication error is considered a "near-miss." Consider this example:

> An order for a fourth dose of medication to be administered to a patient is listed on a medication administration record (MAR). Prior to administration, the pharmacist reviews the chart and notes that the medication was supposed to be discontinued after the third dose. Based on the pharmacist's vigilance, the mistake is averted.

This potential dosing error would be considered a near-miss, because the potential was present for an error but it did not occur and the patient did not receive the incorrect medication.

It is recommended that pharmacists adhere to the following reporting methods for an actual or potential medication error in a confidential and anonymous format:[45]

- ISMP Medication Errors Reporting Program (MERP): 800-233-7767 or https://www.ismp.org/orderforms/ERP_Portal.asp
- U.S. Food and Drug Administration's MedWatch Reporting Program: 800-FDA-1088 or https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm

Once a medication error has been reported, the FDA's Office of Post Marketing Drug Risk Assessment (OPDRA) will review and classify the taxonomy of the medication error using a

system developed by National Coordinating Council for Medication Errors Reporting and Prevention (NCC-MERP).[46] It is important to understand that the FDA receives an abundance of reports on cases and therefore will only review reports that are properly completed. Between 2000 and 2008, the FDA received in excess of 95,000 reports of actual or potential medication errors.[47]

FDA defines serious as any adverse event that is fatal, life-threatening, or associated with a disability, hospitalization or congenital anomaly.[48] The ISMP reports medication errors through a variety of newsletters to ensure that all health care professionals are properly targeted, regardless of their practice setting.[66]

In addition, it is imperative to thoroughly complete all reporting forms to ensure the provision of appropriate data to FDA. Failure to do so may lead to a delay in the investigation of the medication involved and the reasons why the problem occurred, impeding the agency's ability to warn and prevent future episodes. See Table 2 for recent examples of drug safety communication advisories from FDA.[49]

Promoting medication safety

The IOM is the innovative leader in eliciting change in America's medication safety guidelines. Since the IOM released data in 1999 to health care professionals and the public, government agencies such as FDA have collaborated with the IOM to promote change. After the 1999 report, FDA encouraged the IOM to review the current data and provide factual, concrete suggestions to promote medication safety for all Americans. Because errors are preventable, all pharmacists should take responsibility and accountability for all of their actions to ensure medication safety.

In 2006, an IOM report requested that U.S. government agencies take the lead in implementing steps to reduce medication errors, with precise deadlines and recommendations. The IOM estimated that the government should expect to spend $100 million annually to research the most useful and cost-effective ways to reduce medication errors.[36]

The 2006 IOM recommendations (and response to them, where applicable) were:

- FDA and the Agency for Healthcare Research and Quality should be charged with working with the pharmaceutical industry to address problems with drug labels and packaging by the end of 2007 and possibly implement standardized drug names and labels.
    - *FDA acted on this in 2008, shifting increased responsibility to the Office of Surveillance and Epidemiology.*[50]
- By 2008, all health care providers were to develop a plan to transition to electronic prescribing systems.
    - *A report from Office of the National Coordinator for Health IT (June 2012) estimated that 45 percent of new and renewal prescriptions were sent electronically in 2012.*[51]
- By 2010, all health care providers were to begin using electronic prescribing systems.
    - *The same report noted that 48 percent of U.S. physicians now use electronic prescribing systems, compared to only 7 percent in December 2008.*[51]
- The National Library of Medicine should create a central online database for consumers to find information on medications and work with FDA and CMS to consider creation of a nationwide telephone hotline for patients who cannot read printed information.
    - *The National Library of Medicine manages a suite of drug information portals to provide consumers with information on drugs, herbs and supplements.*[52] *Patients can call the FDA Division of Drug Information (DDI) for drug information by telephone at 855-543-3784 or 301-796-3400.*[53]
- All health care providers should report medication errors to patients and family members, regardless of whether harm occurred.
- Pharmaceutical companies should disclose all clinical trial results and limit the practice of providing physicians with free samples of medications because the samples are poorly regulated.
    - *Many scientific journals require the posting of all clinical trials prospectively (as well as results, when available) as a condition for publication. The value of this transparency should strengthen the science and preserve the integrity of the medical literature.*[54] *Although some new limitations are in place, pharmaceutical companies still distribute samples.*
- Pharmaceutical companies should package pills in blister packs to simplify identification and make it easier for consumers to remember whether they took a dose.
    - *Although some medications are contained in blister packages, this is the exception, not the norm.*
- Patients should maintain a list of all prescription and nonprescription treatments that they take and review the document with their health care providers to ensure that there are no potential drug interactions.
- Patients need to become responsible for reading, understanding and abiding by the medication instructions.[60]

Although the IOM has provided many recommendations for U.S. government agencies to implement, the first step in promoting medication safety is to allow and encourage each patient to take a more active role in his or her own medical care. In the past, many patients and their families thought they would be perceived as disrespectful or rude if they questioned their health care practitioner. However, a new way of thinking, according to the IOM 2006 brief report, is to promote a partnership between the health care provider and the patient.

To initiate and implement this paradigm shift, doctors, nurses, and pharmacists need to communicate with patients by listening, consulting and educating them appropriately about each of their medications at various stages of their care.[37]

It is a wonderful idea, but many practitioners argue that restrictive reimbursement by insurance companies, Medicaid and Medicare make it difficult to spend a large amount of time with each patient. Many times, these professionals assume that another professional will spend the quality time that each patient deserves. It is a vicious cycle, but pharmacists can be the leaders in turning it around by promoting quality communication.

The governing agencies encourage health care professionals to keep up-to-date on the latest information on available technological advances. For instance, the IOM states in its 2006 brief report that it is impossible to remember every detail about a medication; therefore, it recommends health care professionals use a point-of-care reference to assess components of the desired medication.[37]

As a result of the IOM recommendations, there have been numerous positive outcomes designed to enhance patient safety. Some examples include:

- The Center for Quality Improvement and Patient Safety (CQuIPS) has been established at AHRQ to integrate patient safety into the broader quality framework, conduct research on how to reduce medical errors, and educate patients about their safety.
- National summits have been conducted, including AHRQ's Patient Safety Research and Practices Summit (September 2000), the Food and Drug Administration's Drug and Device Safety Summit (throughout 2001), and the Department of Veterans Affairs' (VA) Patient Safety Practices (September 2001).

- The Health Care Financing Administration (HCFA, now the Centers for Medicare and Medicaid Services [CMS]) is considering regulations requiring hospitals participating in Medicare to have ongoing medical error programs in place.
- The Office of Personnel Management (OPM) will require all plans in the federal employee health benefits program to seek accreditation that includes the evaluation of patient safety and programs to reduce errors.
- The VA and Department of Defense (DOD) are leaders in computer order entry systems.[55]

Recommendations for improving medication safety during the dispensing phase

It is imperative that pharmacists adhere to the recommendations and guidelines of our governing agencies to improve our medication practices. This can ensure that pharmacists are more conscious about their actions before they dispense a medication to a patient.

All pharmacist programs emphasize the six medication "rights" before administering any medication:

- The right patient.
- The right medication.
- The right dose.
- The right route.
- The right time.

The right documentation. Before dispensing any medication, one of the first precautionary steps to take is to always check the physician's orders against what is known about the patient: What is the disease; are there any concomitant medications that could lead to a drug-drug interaction; does the patient have any co-morbidities that could complicate the use of the medication?

Second, the pharmacist is responsible for verifying that the prescriber has ordered the correct medication at the correct dose, to be administered at an appropriate frequency. Even though there are technologies in place to assess and scrutinize the prescriber's orders, never assume that the available systems will detect a problem or that another colleague verified the order. It is better and safer to check and re-check the order.

Once the medication on the record matches the correct, safe dose that the prescriber ordered, the pharmacist is responsible for ensuring that the correct quantity of the correct medication at the correct dose is accurately provided to the patient at the correct time.

If the pharmacist is not familiar with a medication, he or she should look it up in a drug reference before beginning the process of dispensing the medication. The pharmacist must never assume that the prescriber is fully aware of the medication classification, use, safe dose, side effects, drug-drug interactions, drug-food interactions and other implications. There are so many medications on the market that it is impossible for anyone to fully understand the implications of all drugs that might be prescribed to a patient.

In November 2005, the FDA mandated that all prescription drug information had to be submitted in a searchable electronic format database to provide information for health care professionals and the public.[48]

In January 2006, the FDA revised the format in which prescription drug inserts were to be written and laid out. During that time, the FDA mandated that inserts be written in a clear, concise manner to provide each health care professional the most up-to-date and easy-to-read information to best promote patient safety.[42]

Every year, JCAHO releases the updated National Patient Safety Goals, customized to various inpatient and outpatient settings, to which hospitals and clinics must abide by for accreditation. In June 2007, the board of commissioners at JCAHO approved the 2008 National Patient Safety goals. The third goal involves the safety of medications:

- Identify and, at a minimum, annually review a list of look-alike/sound-alike drugs used by the organization, and take action to prevent errors involving the interchange of these drugs.
- Label all medications, medication containers (for example, syringes, medicine cups, basins) or other solutions on and off the sterile field.
- Reduce the likelihood of patient harm associated with the use of anticoagulation therapy.[56]

Bar code label rule

In February 2004, the FDA issued a final rule requiring bar codes on certain drugs, biologicals and blood product labels.[57] According to 21 CFR 201.25, "manufacturers, repackers, relabelers, and private label distributors of human prescription drug products, biological products, and over-the-counter (OTC) drug products that are dispensed pursuant to an order and are commonly used in hospitals are subject to the bar code requirement, regardless of the method they use to distribute their drug products."[58]

After the initiation of bar codes, the FDA estimated that their implementation would help prevent nearly 500,000 adverse events and transfusion errors, while saving $93 billion in health costs over 20 years.[59]

With the advances in technology, the governing bodies also recommended that facilities incorporate electronic prescriptions by 2010 to avoid mistakes with handwritten prescriptions. Over the years, many pharmacists have complained that physicians' handwriting can be illegible. Pharmacists are trained to verify the medication with the ordering physician instead of making educated guesses about what the doctor meant. The IOM promotes e-prescription software programs because they can also help by assessing for drug allergies, drug-drug interactions and overly high doses during the writing phase to prevent potential medication errors.[37]

According to the Health Care Quality Modernization, Cost Reduction, and Quality Improvement Act, prescribing errors were reduced by 95 percent and hospital costs lowered by 13 percent with automated prescribing. The government has also included e-prescribing adoption in the Medicare Prescription Drug Improvement and Modernization Act of 2003, and many payors are sponsoring e-prescribing initiatives for their providers. E-prescribing can increase patient safety by preventing errors, improving continuity of care, and by tracking and providing feedback about adverse events.[60]

Drug name confusion

FDA collaborates with the ISMP to assess and review potential medications that look alike, sound alike and have labels that could cause a medication error.[61] FDA is adamant about eliminating potential confusion because of the name, appearance or sound of the medication. The goal is to prevent errors during the procurement of a medication. The last time a medication name was changed was in 1994: Levoxine, used to treat hypothyroidism, was often confused with the heart medication Lanoxin. Therefore, FDA recommended a name change. Subsequent to this request, Levoxine was changed to Levoxyl.[66]

It should be noted that after drugs are approved, FDA monitors each medication for errors caused by name confusion. If errors or confusion are noted, FDA informs health care professionals about it in an effort to avoid additional problems. For example, FDA has reported errors involving the administration of methadone instead of the prescribed Metadate ER, (methylphenidate) for the treatment of attention deficit/hyperactivity disorder (ADHD). Unfortunately, there was a case reported where an 8-year-old boy died because the pharmacist filled the opiate, methadone, rather than the intended methylphenidate.[66]

As a pharmacist, it is imperative to recognize the vast array of potential errors from drug name confusion: the data is staggering. In addition, according to Meadows, other examples of drug name confusion reported to FDA include:

- Serzone (nefazodone) for depression and Seroquel (quetiapine) for schizophrenia.
- Lamictal (lamotrigine) for epilepsy, Lamisil (terbinafine) for nail infections, Ludiomil (maprotiline) for depression and Lomotil (diphenoxylate) for diarrhea.
- Taxotere (docetaxel) and Taxol (paclitaxel), both for chemotherapy.
- Zantac (ranitidine) for heartburn, Zyrtec (cetirizine) for allergies and Zyprexa (olanzapine) for mental conditions.
- Celebrex (celecoxib) for arthritis and Celexa (citalopram) for depression.[66]

Drug labeling

In January 2002, a study found that consumers tend to overlook important label information on OTC drugs. Four months later, in May 2002, FDA mandated a standardized "drug facts" label on foods and medications to ensure that consumers have the appropriate information on the product's ingredients, uses, warnings, dosage, directions and proper storage.[66]

For example, during the fall of 2007, news media reports claiming that parents were overdosing their children led many people to believe that cough medications were no longer safe to administer to children under 6 years of age. Pharmaceutical companies responded by changing the labels on all cough medications, telling parents to consult with their doctor before giving a child under 6 years of age the medicine.

In 2000, the FDA proposed a new package insert that was more user-friendly and highlighted the critical information needed for physicians prescribing products.[66] In January 2006, the FDA initiated new changes in the format for the labeling of prescription drugs to provide health care professionals clear and concise prescribing information.[85] The IOM committee recommends that the drug industry and the appropriate federal agencies work together to improve nomenclature, which encompasses drug names, abbreviations and acronyms.[37] It is also is critical to teach patients to recognize that if the medication does not look right based upon its color or shape, they should never assume it is the correct, prescribed medication.[10]

FDA recommendations to improve medication safety

On January 30, 2007, the FDA announced 41 initiatives to improve drug safety based on the recommendations of the IOM.27 Among them were:

- List all products by generic name.
- Do not include the salt of the chemical when expressing a generic name unless there are multiple salts available (i.e., hydroxyzine hydrochloride and hydroxyzine pamoate).
- Use brand names in upper case letters (i.e., LANOXIN, LASIX) to differentiate them from their generic cohort.
- Express suffixes that are part of the brand name (i.e., SR, SA, CR) within both the generic name field and the brand name (i.e., diltiazem XR).
- Avoid the use of all potentially dangerous abbreviations and dose expressions. (See Table 1 – The Do Not Use list.)
- Do not use trailing zeros (5 mg, never 5.0 mg).
- Use leading zeros for doses that are less than 1 (0.3 mg, never .3 mg).
- Spell out the word "units."
- Use the proper, approved standard abbreviations for dosage units.
- Do not abbreviate names (do not use Mso4 for morphine).
- Use upper case and lower case letters (ie., HydrOXYzine and hydrALAZINE) to help distinguish look-alike products.
- When the drug name, strength, dosage form and dosage units appear together, avoid confusion by listing the generic name first and provide a space between them.[62]

Additional recommendations for pharmacists to improve medication safety

In addition to ensuring that the previous recommendations are implemented, pharmacists may be able to participate in implementing the following guidelines to promote patient safety, as incorporated in JCAHO's national safety goal.

In 2006, JCAHO initiated the medication reconciliation form to help prevent medication errors. The medication reconciliation form is implemented upon admission, transfer to another unit, and discharge from the facility to ensure that all home medications and discharge medications are clearly stated to avoid an overlap or drug-drug interactions. The requirements for JCAHO's national safety goals include:

- Implement a process for obtaining and documenting a complete list of the patient's current medications upon the patient's admission to the organization, with the involvement of the patient. This process includes a comparison of the medications the organization provides to those on the list. (Note: While this safety goal does not require a separate form for the medication list, many organizations have found it useful to develop and use one or more forms to support the medication reconciliation process.)
- Ensure that a complete list of the patient's medications is communicated to the next provider of service when a patient is referred or transferred to another setting, service, practitioner or level of care within or outside the organization.[1]

In the second national standard, JCAHO recommended the following to prevent a medication error during the communication phase.[86]

Pharmacists are often required to take verbal orders from a doctor or other prescriber or their representative over the telephone, or sometimes, even in person. Before taking a verbal order over the telephone, the pharmacist should gather all available data about the patient. When given a verbal order, the pharmacist must repeat each component of the order back to the caller, which includes verbalizing the medication and spelling it (if appropriate), reiterating the dose and the frequency of the medication.

Consumers' role to improve medication safety

FDA has been diligently attempting to eradicate or reduce medication errors for patients in a very complex medical system. To promote medication safety, FDA recommends that consumers collaborate with their health care providers to reduce errors. FDA urges consumers to take the following steps:[66]

- As a patient, know the most common type of medication errors that occur. The most vulnerable populations are children and elderly patients over 60 years of age. According to another report in 2007 by FDA, more than 700,000 people go to emergency rooms every year because of a medication interaction. In the same consumer health information form, the FDA said that the most commonly implicated drug causing unexpected medical problems for patients is Coumadin (warfarin).[27]
- Know the name of your medication and its purpose. FDA reiterates that the patient should never take a medication just because "the doctor said so."
- Always read and understand the directions for taking each medication safely and properly as prescribed. According to Weiss (2006), more than 50 percent of patients do not take their medications as prescribed.[10]
- Keep a list of all medications, including OTC, herbals, dietary supplements and any other substances. In addition, patients should continuously review their medications with their primary provider because many people have more than one physician prescribing medications to them. Patients should never assume that their physicians collaborate on care for an individual patient.
- If in doubt, never assume anything. Ask your health care providers for clarification.

To promote medication safety for the consumer, the IOM recommends the following for the pharmaceutical industry:[10]

- The Food and Drug Administration should help standardize the text and design of medication leaflets so that consumers can easily understand them.
- The National Library of Medicine should create a website that is a comprehensive, understandable source of information about drugs and fund a national telephone line for people who don't have Internet access.
- Health care organizations should tell patients about medication errors made in their care, even if they were not hurt by the error.

Goals for the future

Although progress has been made, more providers need to begin using e-prescribing systems, and all pharmacies should be able to receive prescriptions electronically. The Agency for Healthcare Research and Quality (AHRQ) should take the lead in fostering improvements in IT systems used in ordering, administering and monitoring drug usage.

As pharmacists, it is an exciting time to be involved in promoting patient safety by reducing the risks of medication errors. Over the years, governing bodies have made it apparent that they want to reduce and eventually eradicate the risk of patients coming to harm in health care settings. As pharmacists, we must also do our part!

Conclusion

Although there are many variables that lead to medication errors in our complex medical system, there are multiple actions that we can take as pharmacists to promote patient safety. It is imperative to understand the legal responsibilities and obligations that you have to patients you care for directly or indirectly on a daily basis.

Each health care professional can take the initiative and rise above the shortcomings within our health care system to promote patient safety. The governing bodies have provided an abundance of research and evidence-based practice recommendations to prevent and help eradicate the risk of medication errors.

No one ever wants to be a party in a medication error, especially knowing that the errors can be disabling to a patient or even cause death. It takes just a few extra minutes to ensure that each medication is safely prescribed, dispensed and administered to the patient.

Remember: Each patient is an individual who has a story and a family; do not jeopardize his or her safety and life. The next time, it could be your loved one who is the patient.

Table 1: Official "Do Not Use" List[#] by JCAHO

U (unit):	Mistaken for "0" (zero), the number "4" (four) or "cc."	Write "unit."
IU (International Unit):	Mistaken for IV (intravenous) or the number 10 (ten).	Mistaken for IV (intravenous) or the number 10 (ten).
Q.D., QD, q.d., qd (daily):	Mistaken for each other.	Write "daily."
Q.O.D., QOD, q.o.d, qod (every other day):	Period after the Q mistaken for "I" and the "O" mistaken for "I."	Write "every other day."
Trailing zero (X.0 mg)*: Lack of leading zero (.X mg):	Decimal point is missed.	Write X mg. Write 0.X mg.
MS: MSO4 and MgSO4:	Can mean morphine sulfate or magnesium sulfate.	Write "morphine sulfate." Write "magnesium sulfate."

[#] Applies to all orders and all medication-related documentation that is handwritten (including free-text computer entry) or on pre-printed forms.[32]

***Exception**: A "trailing zero" may be used only where required to demonstrate the level of precision of the value being reported, such as for laboratory results, imaging studies that report size of lesions, or catheter/tube sizes. It may not be used in medication orders or other medication-related documentation.

Table 2: Drug safety communications		
April 26, 2013:	Anti-seizure drug Potiga (ezogabine).	Linked to retinal abnormalities and blue skin discoloration.
March 14, 2013:	Incretin mimetic drugs for type 2 diabetes Byetta, Bydureon (exenatide); Victoza (liraglutide); Januvia, Janument, Juvisync (sitagliptin); Onglyza (saxagliptin); Nesina, Kazano (alogliptin); Tradjenta, Jentadueto (linagliptin).	Investigating reports of possible increased risk of pancreatitis and pre-cancerous findings of the pancreas from incretin mimetic drugs for type 2 diabetes.
March 12, 2013:	Zithromax, Zmax (azithromycin).	Risk of potentially fatal heart rhythms.
February 26, 2013:	Sensipar (cinacalcet).	Pediatric clinical trials suspended after report of death.
February 20, 2013:	Codeine.	Safety review update of codeine use in children; new boxed warning and contraindication on use after tonsillectomy and adenoidectomy.
January 10, 2013:	Insomnia drugs containing zolpidem (Ambien, Edluar, zolpimist).	Risk of next-morning impairment after use of insomnia drugs; FDA requires lower recommended doses.
Posted by the FDA January 1, 2012-April 26, 2013		

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PATIENT SAFETY AND MEDICATION ERRORS IN FLORIDA

Final Examination Questions

Select the best answer for each question and then proceed to **EliteLearning.com/Book** to complete your final examination.

1. Which of the following is not a component of a safe medication system?
   a. Administration of the drug.
   b. Preparation and dispensation of the drug.
   c. Selecting the generic equivalent that provides the best profit margin.
   d. Selection and procurement of the drug by a pharmacy.

2. According to the ISMP MERP program, all health care professionals should report actual or potential medication errors that occur due to all of the following factors, except:
   a. Staff misconduct.
   b. Wrong drug, wrong strength, wrong dose.
   c. Errors in transcription.
   d. Calculation errors.

3. Assume the scenario where a prescriber has written an order for three daily doses of lorazepam, 0.5 mg, to be administered at bedtime, with discontinuation after the third dose. When visiting the floor on the fourth night, the pharmacist notes that the nurse has taken a dose of lorazepam from the floor stock, and is preparing to administer it to the patient. The pharmacist immediately recognizes the potential error and stops the nurse from administering the dose. This situation could be described as:
   a. Lucky.
   b. A near-miss.
   c. A pharmacist overstepping his or her responsibility.
   d. A safe and efficient way to run a nursing unit.

4. When determining whether an adverse event is to be considered "serious," FDA requires it to include at least one of the following attributes?
   a. Fatal.
   b. Life-threatening.
   c. Requires a hospitalization.
   d. All of the above.

5. Which of the following was not an FDA recommendation to improve medication safety?
   a. List all products by generic name.
   b. Spell out brand names in lower case to distinguish them from generic names.
   c. Spell out the word "units."
   d. Do not abbreviate names.

Course Code: RPFL02PS

Chapter 2: The Validation of Controlled Drug Prescriptions in Florida (Mandatory)

2 Contact Hours

By: Jodi Dreiling, PharmD, BCPS

Author Disclosure: Jodi Dreiling and Colibri Healthcare, LLC do not have any actual or potential conflicts of interest in relation to this lesson.

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Learning objectives

- Review the role of opioids in the treatment of pain.
- Describe the new Florida laws regarding the dispensing of controlled substances.
- Demonstrate methods to ensure patients with valid prescriptions will have access to controlled substances.
- Discuss the use of a Prescription Drug Monitoring Program (PDMP).
- Assess the therapeutic value of a controlled substance prescription.
- Describe how to detect prescriptions not issued for a legitimate medical purpose.
- Recall prescribing and dispensing controlled substance laws and rules.

Introduction

Florida has become the center of the prescription drug abuse crisis. The increase in opioid prescriptions has been linked to the increase in opioid overdoses. Pharmacists are on the front line for prevention. Increasing knowledge and stricter controlled substance laws can help prevent opioid overdoses. Pharmacists are the last line of defense when evaluating a prescription to ensure its validity.

Opioid epidemic

The United States is battling an opioid overdose epidemic. Opioids are commonly prescribed for pain, with approximately 20% of patients receiving an opioid prescription to treat a pain-related diagnosis (Daubresse, 2013). In 2012, there were 259 million prescriptions written for opioid pain medication, which is enough for every adult in the United States to have a bottle of pills (Paulozzi, 2014).

Opioid pain medications have serious risks, including overdose and addiction. In 2015, 12.5 million people misused prescription medications (Hughes, 2016). The increased rate of prescriptions has correlated with the increase rate of deaths. In 2015, over 33,000 people died from overdosing on opioids (Rudd, 2016). Unfortunately, this number may be grossly underestimated as the CDC relies on death certificate codes for data. These codes do not reflect the cause of death, and only reflect the conditions that exist at death. The overdose deaths reported by the CDC are based only on data from 28 states that have high quality reporting (Hughes, 2016).

The number of deaths from opioids is rapidly increasing in Florida. In May 2017, the Medical Examiners Commission released an interim report reviewing overdoses from the January through June 2016. In 2016, the number of total drug-related deaths increased by almost 14% when compared to 2015. Over 3,000 people died with one or more prescription medication in their system, which was 466 more deaths than in 2015. Prescription drugs were identified as the cause of death in 1,616 individuals in the first half of 2016, which was 440 more deaths compared to the first half of 2015. The most concerning increase was the frequency of death due to fentanyl overdose, occurring in 704 individuals. The number of deaths caused by fentanyl increased by 139.5% (an increase of 410) compared to 2015. The medications causing the most deaths were: fentanyl, benzodiazepines, morphine, oxycodone, and methadone (FME, 2017).

In May 2017, the governor of Florida declared a statewide Public Health Emergency for the opioid epidemic. This Emergency Order allows Florida to gain 27 million dollars in federal grant funding from the United States Department of Health and Human Services Opioid State Targeted Response Grant. The federal grant will assist communities in providing prevention, treatment, and recovery services (State of Florida, 2017).

In August 2017, the president of the United States declared the opioid crisis a National Emergency. Declaring a National Emergency allows certain federal rules to be waived. Also, it allows states and cities that are hit the hardest by the opioid crisis to receive federal relief funds and other types of urgent aid (White House, 2017).

Opioid overdose prevention

Improving the way that opioids are prescribed through clinical practice guidelines can ensure patients have access to safer and more effective chronic pain treatment. Following clinical practice guidelines can also help reduce the number of people who misuse, abuse, or overdose from controlled substances (Olsen, 2016).

The Center for Disease Control and Prevention developed guidelines in 2016 to provide recommendations for the appropriate prescribing of opioids in chronic pain. These guidelines were targeted towards primary care clinicians who are prescribing opioids for chronic pain outside of active cancer treatment, palliative care, or hospice patients. Chronic pain is defined as pain that lasts more than 3 months or past the time or normal tissue healing. Chronic pain can be the result of an underlying medical condition or treatment, injury, inflammation, or unknown cause (Dowell, 2016).

Clinicians are advised that non-pharmacological and non-opioid pharmacological therapies are preferred for chronic pain. Prescribers should only consider opioid therapy if the therapy benefits outweigh the risks. If opioids are utilized, they should be prescribed only in combination with non-pharmacological or non-opioid therapy (Dowell, 2016).

Figure 1: Examples of alternative therapies

Non-opioid pharmacological therapies	Acetaminophen NSAIDs (i.e. ibuprofen, meloxicam, naproxen) Anticonvulsants (i.e. pregabalin, gabapentin, carbamazepine) Antidepressants (i.e. duloxetine, tricyclics)
Non-pharmacological Therapies	Exercise Cognitive behavioral therapy Physical therapy

The guidelines advise that a prescriber establish realistic treatment goals with the patients, including a discontinuation plan if the benefits do not outweigh the risks. The prescriber should initiate opioid therapy with immediate release opioids instead of extended release or long-acting opioids. Long-acting opioids have an increased risk for overdose and should be reserved for patients with pain severe enough to require daily, around the clock, long-term opioid therapy (Dowell, 2016).

When opioids are started, the lowest effective dose should be utilized. Prescribers are advised to use caution when increasing doses above 50 morphine milligram (MME) equivalents per day. Clinicians are advised to avoid increasing dosage to > 90 MME/day or to carefully justify that dosage titration. Higher doses of opioids have been associated with increased risk of motor vehicle injury, opioid use disorder, and overdose. For doses of 100 MME and higher, the risk of overdose increases by 2 – 8.9 times (Dunn, 2010). The guidelines and experts agreed that increasing the dose above 50 MME increased overdose risk without adding benefit for pain relief.(Manchikantl, 2017) Prescribers should consider tapering patients who have been established on higher doses of opioids, considering the recent evidence regarding the association of opioid dose with overdose risk (Dowell, 2016).

When treating acute pain, clinicians are advised to prescribe the lowest possible effective dose of immediate-release opioids and not to prescribe a quantity that is greater than needed. The guidelines recommend that a 3 day supply of medication (or less) is often sufficient, and that more than a seven day supply is rarely needed. When practitioners prescribe opioids for chronic pain, patients should be evaluated within 1 to 4 weeks to review the benefits and harms of opioid therapy. Patients should be seen by the prescriber every 3 months (or more frequently) to review the appropriateness of continued opioid therapy (Dowell, 2016).

The CDC guidelines recommend that opioids and benzodiazepines should not be prescribed concomitantly whenever possible. They both can decrease the respiratory drive and put patients at a higher risk for potentially fatal overdose (Dowell, 2016).

Naloxone

There are many risks of using opioid therapy. The CDC guidelines recommend that naloxone should be offered to patients who are at a high risk for overdose. Overdose risk is increased in patients with a history of overdose, history of substance abuse, higher doses of opioid therapy (> 50 MME/day), or concurrent benzodiazepine use (Dowell, 2016). Other types of patients that may be at higher risk for overdose include:

- Sleep-disordered breathing (i.e. sleep apnea).
- Pregnancy.
- Renal or hepatic disease.
- Age > 65 years of age.
- Concomitant mental health conditions.

In 2016, Florida enacted the "Emergency Treatment and Recovery Act" which allows health care providers to prescribe and dispense opioid antagonists (i.e. naloxone) to patients, care givers, and first responders without a prescription. Pharmacists are allowed to dispense naloxone to patients and caregivers based on a non-patient-specific standing order. Naloxone may be delivered either by means of the auto injection delivery system or by intranasal application. As with all prescriptions, naloxone must be properly labeled with instructions for use. This rule allows patients and caregivers to store and possess naloxone, and administer it to a person believed to be experiencing an opioid overdose, regardless of whether the person has a prescription for the agent. Pharmacists are protected from civil liability via the Good Samaritan Act as long as they act in good faith and exercise reasonable care (FLA. STAT §381.877).

Pharmacist who dispense naloxone must keep a copy of the Naloxone Standing order. There are 3 approved options for naloxone (State of Florida, Office of the State Surgeon General, 2017).

Figure 2: Naloxone standing order options

Medication	Directions for Use
Naloxone 2mg/2mL prefilled syringes #2 Mucosal Atomization Device #2	Spray one-half of the syringe into each nostril upon signs of an opioid overdose. Call 911. May repeat x 1
Naloxone 0.4mg/0.4mL #1 twin pack	Use one auto-injector upon signs of an overdose. Call 911. May repeat x 1
Narcan Nasal Spray 4mg, #2	Administer a single spray intranasally into one nostril. Call 911. Administer additional dose using a new device for each dose if patient does not respond, or responds and then relapses into respiratory depression. Additional doses may be given every 2-3 minutes until emergency medical assistance arrives.

The Naloxone Standing Order is the expectation that the Opioid Overdose Prevention Toolkit developed by the Substance Abuse and Mental Health Services Administration will be followed. When dispensing naloxone to a patient or family member, pharmacists should counsel them on the appropriate use. There are 5 key points that should be highlighted during counseling (SAMHSA, 2016):

The risk of serious side effects with naloxone is rare. The most common side effect of naloxone is opioid withdrawal. Common opioid withdrawal symptoms include aches, irritability, sweating, runny nose, diarrhea, nausea, and vomiting. The risk of opioid overdose outweighs the potential opioid withdrawal symptoms (SAMHSA, 2016).

Figure 3: Opioid overdose counseling points (SAMHSA, 2016)

1. Call 911
- Opioid overdoses will require professional medical assistance even if naloxone helps.

2. Check for signs of an overdose
- Extreme sleepiness, inability to wake.
- Breathing problems, shallow breaths, slow breathing pattern.
- Fingernails/lips turning blue.
- Extremely small pupils (pinpoint).
- Slow heartbeat/low blood pressure.

3. Support the patient's breathing
- Ensure that the patient's airway is clear (nothing in mouth).
- Place one hand on the patient's chin, tilt the head back and pinch the nose close.
- Place your mouth over the patient's mouth to make a seal and give 2 slow breaths.
- The patient's chest should rise (not the stomach).
- Give one breath every 5 seconds.

4. Administer naloxone for signs of an overdose
- Naloxone should be given to restore respiratory drive.

Defining the problem

About 25% of patients diagnosed with chronic pain misuse or abuse opioids, up to 12% of chronic pain patients are addicted to their opioids. There is a lack of consensus on the terminology surrounding pain therapy, abuse, and misuse. While there is no standardization, these are the most commonly used definitions (ACPM, 2011).

Abuse: Self-administering medications to change one's state of consciousness (i.e., getting high). This is an intentional, maladaptive pattern of use of a medication (whether legitimately prescribed or not) leading to significant impairment or distress—such as repeated failure to fulfill obligations, recurrent use in situations in which it is physically hazardous, multiple legal problems, and recurrent social and interpersonal problems—occurring over a 12-month period.

Addiction: A primary, chronic, neurobiological disease, with genetic, psychological, and environmental factors influencing its development and manifestations. Addiction is characterized by the 4 C's—(behaviors that include one or more of the following): impaired control over drug use, compulsive use, continued use despite harm, and craving.

Dependence: The manifestation of a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.

Diversion: Redirection of a prescription drug from its lawful purpose to an illicit use.

Misuse (noncompliant use): The intentional or unintentional use of a prescribed medication in a manner that is contrary to directions, regardless of whether a harmful outcome occurs.

Overdose: When a drug in swallowed, inhaled, injected, or absorbed through the skin in excessive amounts and injures the body. Overdoses are either intentional or unintentional.

Physical dependence: A state of adaptation manifested by a drug class-specific withdrawal syndrome that occurs by abrupt cessation of a drug, rapid dose reduction, decreasing levels of the drug in the blood, and/or administration of an antagonist resulting in dysphoric signs and symptoms generally the opposite of the desired drug effect, and tolerance defined by adaptation so that that increasing doses of a drug is needed to achieve the same desired effect.

Tolerance: A state of adaptation in which exposure to a given dose of a drug induces changes that result in diminution of one or more of the drug's effects over time.

Withdrawal: A variety of unpleasant symptoms (e.g., difficulty concentrating, irritability, anxiety, anger, depressed mood, sleep disturbance, and craving) that occur after use of an addictive drug is reduced or stopped. Withdrawal symptoms are thought to increase the risk for relapse.

Pathophysiology of opioid addiction

The pathophysiology of opioid addiction can be explained by the mechanism of action of opioids and receptor activity. Opioid receptors are located throughout the central nervous system and in the peripheral tissues. Opioid receptors are stimulated endogenously in response to external inflicted pain and exogenously when an opioid agonist is ingested. Depending on the opioid consumed, a patient will feel pain relief in combination with pleasure and reward. There are 3 opioid receptors that have clinically relevant actions:

- Mu receptors: analgesic effects, respiratory depression, sedation, decreased bowel motility, euphoria, and physical dependence.
- Kappa receptors: analgesic effects, sedation, dyspnea, dysphoria, respiratory depression, physical dependence.
- Delta receptors: psychiatric symptoms, dysphoria.

Activation of the Mu receptors triggers the release of dopamine into the reward pathway. Dopamine is the main component of dependence as it regulates emotion, motivation, feelings of pleasure and reward. Some individuals may be predisposed genetically to addiction. They may have a lower expression of dopamine receptors, and self-medicated with a drug of abuse to compensate for this deficiency (Compton, 2016).

Conversion of morphine milligram equivalents

Calculating the total daily dose of opioids helps identify patients who may benefit from closer monitoring, reduction or tapering of opioids, prescribing of naloxone, or other measures to reduce the risk of overdose. The following steps should be used to convert to morphine milligram equivalents:

1. Determine the total amount of daily opioid that a patient takes.
2. Convert to MMEs – multiple the dose of each opioid by the conversion factor in the table.
3. Add them together.

The dose calculated should not be used to convert from one opioid to another. There are multiple factors that need to be taken into consideration, including cross-tolerance, opioid pharmacokinetics, and dose adjustments.

Figure 4: Opioid conversion (CDC, 2017)

Opioid (doses in mg/day except where noted)	Conversion Factor
Codeine	0.15
Fentanyl Transdermal (mcg/hr)	2.4
Hydrocodone	1
Hydromorphone	4
Methadone 1-20mg/day	4
Methadone 21-40mg/day	8
Methadone 41-60mg/day	10
Methadone >61-80mg/day	12
Morphine	1
Oxycodone	1.5
Oxymorphone	3

Case study

Mrs. Penny brings a prescription for Oxycodone ER 10mg PO BID #60 and Hydrocodone 7.5mg/325 PO q6hr prn #120. This is the first prescription she has filled at your pharmacy and is the only prescription on E-FORCSE.

1. What is Mrs. Penny's total MME?
   Oxycodone = 20mg/day
   20mg x 1.5 = 30mg/day MME

   Hydrocodone = 30mg/day (maximum potential)
   30mg x 1 = 30mg/day MME

   Oxycodone 30mg MME + Hydrocodone 30mg MME = 60mg MME

2. What should you do next?
   a. Dispense both medications, no questions asked.
   b. Do not fill either prescription, the doses are too high.
   c. Fill only the hydrocodone.
   d. Discuss with Mrs. Penny her history and indication.

Correct Answer: d.

When speaking with Mrs. Penny, you find out that she was recently in the hospital for 2 weeks after a traumatic fracture. She was titrated up to these doses by her pain management specialist. After discussing the risks of these medications, you dispense them as ordered.

High risk patients for overdose

Patients who are identified as a high risk for overdose should have extra monitoring, education, and access to naloxone. Pharmacists can assist with all of those points, including identifying patients at high risk for overdose. There are multiple screening tools that can be utilized to look for potential risk of addiction, but there are other risk factors that should be considered (Manchikantl, 2017):

- Recent hospitalization for opioid overdose or poisoning.
- History of injection drug use.
- Suspected or confirmed heroin abuse or nonmedical opioid abuse.
- Enrolled in buprenorphine or methadone maintenance or detoxification program.
- High-dose opioid prescriptions (> 50 mg morphine equivalents per day).
- Use of extended release or long-acting preparations.
- Opioids with concomitant: smoking, COPD, emphysema, asthma, sleep apnea, respiratory disorder, alcohol use, concurrent benzodiazepine use.

Patient counseling for overdose prevention

Pharmacists play an essential role in the prevention of overdose. Pharmacists can counsel patients on the risk opioids as clinical pharmacists in the hospital or at the time of dispensing in a community setting. Pharmacists can help identify patients that are at a high risk of overdose, and potentially intervene, preventing a death. There are several counseling points that should be included (Bailey, 2014):

- Only take opioids prescribed for them and according to labeled directions.
- If they become worried about their opioid use, call their pharmacy or healthcare provider.
- If they are not taking their medications properly, a healthcare provider can help them revise treatment.
- Always provide their prescriber with an updated medication list.
- Do not mix opioids with alcohol or other mediations. Contact their pharmacist to make sure that other medications they are taking are safe to take while taking opioids.
- Store opioids in a safe and secure place and dispose of any used medication.
- If they stop taking opioids, a lower dose may be needed upon restarting to prevent overdose.
- Teach friends and family on how to recognize an overdose and how to respond, including where any naloxone is stored.

Opioid storage and disposal

Patients should be reminded that controlled substances should be stored out of the reach of children and pets. In addition, they should be in a safe location, preferably locked, to ensure other family members and visitors are unable to take them.

The Centers for Disease Control and Prevention recommends healthcare providers discuss the risks of intentionally or unintentionally sharing opioids with others for whom they are not prescribed, including the potential for overdose.

In addition, pharmacists can remind patients of appropriate ways to dispose of unused opioids. The preferred option is to utilize a local "take back" or mail-back program. Local take back programs can be found using the DEA's search utility, found at https://apps.deadiversion.usdoj.gov/pubdispsearch/spring/main?execution=e1s1 (AMA, 2017).

If a local drug take back program is not an option, patients can mix their unused medications with an unpalatable substance, such as coffee grounds or kitty litter, in a container that can be thrown in the trash (AAP, 2018).

Florida's efforts against opioid overdoses

In order to curb overdoses, Florida Office of the Attorney General developed a road map to shut down "pill mills." The coordinated plan had 3 goals in order to increase the fight against illegal opioid use. They wanted to reduce the supply of illegal prescription drugs, decrease the demand for diverted drugs, and protect the patient's privacy and rights to access their schedule prescription drugs. This requires a balancing act between decreasing controlled substance diversion, while maintain patient access (The State of Florida, Office of the Attorney General, 2012).

To help decrease the "pill mills" and assist with the illegal supply of prescription drugs, the Florida State Board of Pharmacy has modified its regulation establishing standards of practice for the filling of controlled substance (§64B16-27.831).

NEW FLORIDA PHARMACY LAWS

Florida controlled substance continuing education requirement

All Florida pharmacists must complete a 2 hour Pharmacy Board approved continuing education program on the Validation of Prescriptions for Controlled Substances. The course content must include the following:

- Ensuring access to controlled substances for patients with a valid prescription.
- Use of the Prescription Drug Monitoring Program's Database.
- Assessment of prescription for appropriate therapeutic value.
- Detection of prescriptions not based on a legitimate medical purpose.
- Laws and rules related to the prescribing and dispensing of controlled substances.

The continuing education must be completed during the biennium ending on September 30, 2019. A 2 hour controlled substance continuing education course must be completed every 2 years thereafter. The controlled substance continuing education may count towards the mandatory 30 hours of continuing education required for licensure renewal (§64B16-27.831).

Ensuring patient access

According to Florida Law, validating a prescription means the process implemented by the pharmacist to determine that the prescription was issued for a legitimate medical purpose. Each prescription may require a different validation process. There are different circumstances that may lead a pharmacist to question the validity of the prescription. However, Florida states that a concern with the validity of the prescription does not mean that the prescription should not be filled. Rather, the pharmacist shall attempt to determine the validity of the prescription and resolve any concerns about its validity by exercising their professional judgment (§64B16-27.831).

Pharmacists should not fear disciplinary action from the State Board of Pharmacy or other regulatory enforcement agencies for dispensing controlled substances for a legitimate medical purpose in the usual course of professional practice. Each individual and prescription should be reviewed for validity. The pharmacist should work with the patient and prescriber to determine the validity of the prescription (§64B16-27.831).

Figure 5: Definition of a prescription validity

Valid Prescription	A prescription is valid when it is based on a practioner-patient relationship and when it has been issued for a legitimate medical purpose.
Invalid Prescription	A prescription is invalid if the pharmacist knows or has reason to know that the prescription was not issued for a legitimate purpose.

Validating a prescription

When a Florida pharmacist is validating a prescription, there are 3 things that must be completed:

1. Neither a person nor licensee shall interfere with the exercise of the pharmacist's independent professional judgment.
2. All communication with the patient shall not be overheard by others.
3. If the pharmacist determines in their professional judgment that there are concerns with a prescription's validity cannot be resolved, the pharmacist shall refuse to fill the prescription.

Minimum standards before refusing to fill a prescription

Before refusing to fill a prescription, the pharmacist shall attempt to validate the prescription by performing the following:

1. Initiate communication with the patient or the patient's representative to acquire information relevant to the concern with the validity of the prescription.
2. Initiate communication with the prescriber or the prescriber's agent to acquire information relevant to the pharmacist's concern with the validity of the prescription.
3. In lieu of either 1 or 2, but not both, the pharmacist may elect to access the Prescription Drug Monitoring Database to acquire information relevant to the pharmacist's concern with the validity of the prescription.

Florida law on patient identification

Prior to dispensing a Schedule II, III, or IV controlled substance, a pharmacy must verify the legal name, address, and birthday of the patient receiving the prescription. The patient needs to provide the pharmacy with a government identification card (§893.04).

Prescription validity and red flags

Prior to filling a prescription, a pharmacist must look for "red flags" that call a prescription into question. Such warnings require the pharmacist to carefully review and resolve the red flags prior to dispensing the prescription. The pharmacist should review the prescription and the patient behavior (NABP, 2015).

Prescription validity

- When reviewing the prescription, does it look valid or dose it raise reasonable suspicion of its validity?
- Does the prescription look "too good"? Is the prescriber's handwriting too legible?
- Does the prescription appear to be photocopied?
- Are the abbreviations used accurately or is the prescription written out without abbreviations?
- Is the prescription a drug cocktail or combination of 3 common drugs: opiate, benzodiazepine and muscle relaxant?
- Is this a normal dose of the controlled substance?
- Does the patient record reveal multiple prescribers? Could this patient be doctor shopping?
- Was the prescription prescribed at a distant location?
- Does this prescriber write more prescriptions (or larger quantities) compared to other prescribers?

Patient behavior

- Do you notice any unusual behaviors by the patient, including slurred speech, lack of balance, pinpoint pupils?
- Does the patient refer to the medication with "street slang?"
- Are multiple patients receiving the same controlled substance regardless of weight or age?
- Did multiple patients come in as a group, all with the same prescriber?
- Did the customer pay cash for an opioid? Did the patient want to pay cash for some prescriptions and insurance for others?

Case study

A new patient, Miss Jenny Ryder, brings a prescription to your pharmacy right before closing time. She gives you the nicely typed prescription. Miss Ryder states that she will wait for the prescription and will pay cash. After looking up Miss Ryder in your computer system, you discover it is her first prescription with your store and she is from out of state. The prescription is for Hydrocodone/Acetaminophen 7.5/325 #60 Take one tablet every 6 hours as needed. The prescription is written by a physician located about 3 hours away from your store. After reviewing Miss Ryder's PMDP, you see that she has more than 25 prescriptions by 10 different doctors in the last 6 months.

What are some items that may be red flags for this prescription?

- First time customer from out of state.
- Prescriber is located more than 3 hours away from the pharmacy.
- Multiple prescribers and pharmacies.
- Presented right before closing time.
- Prescription too neat, no abbreviations.

Fraudulent prescriptions

The dispensing pharmacist must maintain constant vigilance against forged or altered prescriptions. The law holds the pharmacist responsible for knowingly dispensing a prescription that was not issued in the usual course of professional treatment. There are many ways that a person can fake a prescription. Here are some items that a pharmacist should be on the lookout for:

- Stolen prescription pads from a prescriber and then prescriptions written for fake patients.
- Legitimate prescriptions altered by the patient (i.e. 10 turned into 100).
- Prescription pads printed with different call back phone numbers.
- Fake doctors, DEA numbers, and phone numbers that all may appear legitimate.

If a pharmacist thinks that they have a fraudulent prescription, they should immediately contact the police department (NABP, 2015).

Prescription drug monitoring programs

Prescription Drug Monitoring Programs (PDMPs) are state based electronic databases that contain information on controlled substance prescriptions dispensed by pharmacies and prescribers. These programs can help decrease the misuse and diversion of controlled substances. Various users have access to PDMPs. Each type of user can utilize the PDMP in a different way to help curb illegal controlled substance use (Perrone, 2012).

Uses of PMDP:

- Prescriber/Pharmacist: check patient's profile for aberrant or consistent controlled substance use.
- Licensing board: use data to identify aberrant prescribing patterns by practitioners.
- Criminal Justice systems: utilize data for drug diversion investigations.
- Insurers: data provides complete picture of dispensed controlled substances (i.e. cash prescriptions).
- State officials: aggregate data to develop and implement targeted health interventions (i.e. prescriber education campaigns).
- Researchers: track prescribing trends and risks using de-identified data.

The Electronic-Florida Online Reporting of Controlled Substance Evaluation program (E-FORCSE) is Florida's PDMP. E-FORCSE was created in 2009 to encourage safe prescribing and reduce drug abuse and diversion. Health care practitioners in Florida are not required to use the PMDP prior to prescribing or dispensing a controlled substance, but are strongly encourage to use the database. The E-FORCSE database collects and stores prescribing and dispensing data for controlled substances in Schedules II, III, and IV. As of January 1, 2018, prescription information must be reported as soon as possible, but no later than the close of business the next day. If there are no dispensing transactions, a zero report must be disclosed. (PEW Charitable Trusts, 2016).

The following data must be sent to the PDMP:

- The name of the prescribing practioner, the practioner's DEA registration number, the practioner's National Provider Identification or other appropriate identifier.
- Date of issuance of the prescription.
- Date the prescription was filled and the method of payment (i.e. cash, insurance, Medicaid).
- Full name, address, and date of birth for the patient the prescription was written for.
- Name, national drug code, quantity, and strength of the controlled substance dispensed.
- Full name, federal Drug Enforcement Agency Registration number, and address of the pharmacy or other location where the controlled substance was dispensed.

E-FORCSE allows practioners and pharmacists, and their designees access to look up, view and print controlled dispensing information on their specific patients. Access is only allowed to individuals, and not to clinics, hospitals, pharmacies, or other health care facilities. A pharmacist or practioner may link designees to their account to grant them access to the E-FORCSE program. This allows the designee to obtain information about the patient on the behalf of the prescriber or pharmacist.

As of March 31st, 2017, over 216 million controlled substance dispensing records have been reported to the PDMP since it began collecting data in September 2011. Over 94% of pharmacies are in compliance with the reporting requirements. Among all licensed health care providers, pharmacists have the highest registration rate, 57.7%. Additionally, pharmacists have the highest utilization rate (91.3%) and have used the database over 18 million times (E-FORCSE, 2017).

PDMPs are likely contributing to the overall decline in drug diversion and prescription opioid overdoses, though the true effect is difficult to determine. Evidence to support the effectiveness of PDMPs comes from observational studies or provider surveys (Griggs, 2015). The E-FORCSE program has shown some success. The number of patients receiving a controlled substance from 5 or more prescribers and having a controlled prescription from 5 or more pharmacies has decreased by 72% since 2012. While there has been an increase in deaths from opioids, the rate of deaths from Oxycodone in Florida decreased by 42% between 2014 and 2015 (E-FORCSE, 2017).

Information in PDMPs is of the puzzle pieces that a pharmacist uses to determine whether a controlled substance prescription is valid. Information in the PDMP should not be the sole determining factor when making a decision to fill a particular prescription. The information in the PDMP could contain data entry errors. Potential errors that could mislead a user of the PDMP include: wrong patent date of birth or address, misspelled patient name, wrong day supply entered, filled under wrong physician, or prescription updated but updated information not sent to PDMP (Griggs, 2015).

When assessing the PDMP, there are multiple items that a pharmacist can evaluate to help guide the interpretation of prescription validity. Those items include (NABP, 2015):

1. Prescriber
   - Is the prescriber consistent?
   - Are there multiple prescribers?
   - Is the patient utilizing urgent care centers, emergency rooms, dentists?
   - Is the prescriber located within 25 miles of the pharmacy?
   - Does the prescriber have known/pending legal issues (i.e. DEA/medical board)?
   - Is the prescriber a pain management specialist?
   - Is the medication within the scope of the prescriber (i.e. dentist prescribing long- acting opioid)
2. Prescription
   - What are the types of controlled substances being used?
   - Are there opioid and benzodiazepine cocktails every month?
   - Are the doses or quantities escalating?
   - Are the medications getting filled early consistently?
   - Are the quantities consistent or are they small amounts each month?
   - Does the dose appear to be tapered off by one prescriber?
3. Pharmacy/Payment
   - Is the same pharmacy being utilized consistent or are there different ones each fill?
   - Is the payment method consistent or does it vary between cash and insurance?
   - Is the patient requesting that the prescription not be submitted to insurance?

Case presentation

Patient Case #1

Mr. Miller is a 27-year-old male who arrives at the pharmacy 1 week early to fill his alprazolam. His medication profile shows past prescriptions for oxycodone 5mg, carisoprodol 350mg, and fluoxetine 20mg. You notice that his prior refills for oxycodone and carisoprodol are consistently 5 days early. When questioning Mr. Miller about his early refill request, he states that his prescription was stolen. He also mentions that his "Oxys" might have been stolen too.

Should you refill his prescription early? If Mr. Miller could produce a police record with the stolen alprazolam mentioned, it could be considered. However, Mr. Miller's consistent early refill pattern shows that he may have a substance abuse problem. Also, Mr. Miller appears to be using slang terms to describe his medications (See Figure 5).

Figure 5: Street names for prescription medications

Opioid	Street name
Codeine	Captain Cody, Syrup, Schoolboy
Fentanyl	Apache, China girl, Dance fever, Friend
Heroin	Smack, Dope, Junk, Black Tar, Dragon, White China
Hydrocodone	Vikes, Watson-387, Norco, Hydro
Hydromorphone	Juice, Smack, Dillies
Morphine	Black Mollies, Black Pill, Tango and Cash, TNT, Murder 8, Morph
Oxycodone	Oxy, Ox, OC, Hillbilly heroin, Percs, Oxycotton
Oxymorphone	Blue heaven, Blues, Octagons, Stop signs, Pink, Pink Heaven, The O Bomb

Management of the Florida Prescription Drug Monitoring Program

Every pharmacy shall maintain a computerized record of every controlled prescription dispensed. The pharmacy must electronically transmit dispensing information to the program's database as soon as possible, but no more than close of the next business day after the controlled substance is dispensed.

There are several acts of dispensing or administration that are exempt from reporting to the Florida PDMP (§893.055):

- Health care provider administering the controlled substance directly to a patient.
- Patients receiving care in a hospital, emergency room, nursing home, ambulatory surgical center, hospice, intermediate care facility for the developmentally disabled.
- Health care practioner administering or dispensing to a patient in the Department of Corrections.
- Health care practitioners when administering or dispensing to a person under the age of 16.

- A pharmacist or dispensing practioner when dispensing a one time, 72 hour emergency resupply of a controlled substance to a patient.
- When a state-declared or nationally declared disaster suspends reporting.

Florida pharmacy summary record

A hard copy printout summary of the controlled substance record, covering the previous 60 days, shall be made available within 72 hours following a request for it by law enforcement personnel. The summary record shall include information from which it is possible to determine the volume and identity of controlled substance being dispensed under the prescription of a specific prescriber and the volume and identity of controlled substance being dispensed to a specific patient (§64B16-27.831).

Florida prescriber diversion

If a pharmacist has a reason to believe that a prescriber is involved with the diversion of a controlled substance, they are required to report the prescriber to the Department of Health. The pharmacist can file a claim at www.flhealthcomplaint.gov (§64B16-27.831).

Controlled Substance Act (CSA)

In 1970, President Richard Nixon signed the Comprehensive Drug Abuse Prevention and Control Act into law. This legislation created the Controlled Substance Act (CSA), which regulates the manufacturing, importation, possession, use, and dispensing of controlled substances The CSA categorized medications into five schedules based on medical benefits and abuse potential. The CSA establishes security and record keeping requirements, provides that a pharmacist has corresponding responsibility when dispensing controlled substances, establishes what constitutes a valid prescription, and limits dispensing requirements (DEA, 2012).

The U.S. Drug Enforcement Agency (DEA) implements and enforces the CSA. The DEA regulates controlled substance schedules and registration of manufacturers, distributors, and dispensers of controlled substances. They also regulate the import and export of controlled substances. The DEA may prosecute anyone that violates this law (DEA, 2012).

Who may issue prescriptions

A prescription for a controlled substance may only be issued by a physician, dentist, podiatrist, veterinarian, mid-level practitioner, or other registered practitioner who is:

1. Authorized to prescribe controlled substances by the jurisdiction in which the practitioner is licensed to practice.
2. Registered with the DEA or exempted from registration (e.g., Public Health Service, Federal Bureau of Prisons, or military practitioners).
3. An agent or employee of a hospital or other institution acting in the normal course of business or employment under the registration of the hospital or other institution that is registered in lieu of the individual practitioner being registered provided that additional requirements as set forth in the Code of Federal Regulation are met (DEA, 2012).

MIDLEVEL PRACTIONER PRESCRIBING CONTROLLED SUBSTANCES – FLORIDA LAW

While the CSA allows nurse practitioners and physician assistants to prescribe controlled substances, each state has different regulations. The physician assistant must be delegated the authority to prescribe controlled substance by their supervising physician. Physician assistants and nurse practitioners have no limits on the number of controlled substances Schedule III-V that they may write; however, they may only write a 7 day supply of schedule II medications. The 7 day supply of schedule II medication does not apply to psychotropic medications for children under the age of 18 prescribed by a psychiatry practitioner. Practitioners are advised not to write multiple 7 day supplies of medications for patients to circumvent the system (§464.012, §458.347).

Federal laws on prescribing controlled substances

Prescriptions may be presented to the pharmacy via a hard copy (paper), verbal (oral) or via an electronically. According to federal law, a prescription for a controlled substance must include the following information (21 CFR 1306.05[a]):

- Date of issue.
- Patient's name and address.
- Practitioner's name, address, and DEA registration number.
- Drug name.
- Drug strength.
- Dose form.
- Quantity prescribed.
- Directions for use.
- Number of refills (if any).
- Manual signature of prescriber.

If a prescriber is going to use a hard copy prescription, the prescription must be written in ink, indelible pencil, or type written and then manually signed by the practitioner. The law states that an individual (i.e. secretary or nurse) may prepare the prescription for the practitioner's signature; however, the practioner is responsible for verifying that the prescription follows all the legal requirements. The signature should be the same manner as the practioner would sign a check or legal document (DEA, 2012).

Electronic prescriptions for controlled substances

Practitioners may write prescriptions for controlled substances electronically. The DEA has very specific requirements for the pharmacy and prescriber to certify that the e-prescribing system is valid. The DEA requirements are set forth in 21 CFR 1311. A pharmacy may process electronic prescriptions for controlled substances if they use a pharmacy application that meets all of the applicable requirements of 21CFR 1311 and is in conformity with the requirements of the controlled substance act.

When a pharmacist receives a paper or oral prescription that shows that it was originally transmitted electronically to another pharmacy, the pharmacist must check with the pharmacy's records to ensure that the electronic version was not dispensed. If both prescriptions were received, the pharmacist must mark one as void.

If a pharmacist receives a paper or oral prescription that was electronically transmitted to another pharmacy, the pharmacist must check with that pharmacy to determine if the prescription

was received and dispensed. If the pharmacy that received the original electronic prescription has not dispensed the prescription, the pharmacy must mark the electronic version as void/cancelled. If the pharmacy that received the electronic prescription dispensed the prescription, the pharmacy with the paper version must not dispense the paper prescription and mark the prescription as void/cancelled (DEA, 2012).

Case study

Mr. Smith brings a prescription for Percocet 5/325 #60 Take 1 tablet every 6 hours as needed for pain to your pharmacy, "Pharmacy A." The prescription appears to be an electronically prescribed prescription; however, it is signed by the prescriber. After speaking with the patient, he states that the prescriber sent the prescription to "Pharmacy C," but also printed a copy in case they were closed. After reviewing the E-FORCSE website, you see that the prescription was filled at "Pharmacy C." When speaking to the patient, he would still like to get the prescription at your store. Luckily, when you call "Pharmacy C" they are still open.

What would be the appropriate next steps?

a. Do not fill the prescription for Percocet.
b. Fill the prescription for Percocet, and do not tell "Pharmacy C."
c. Fill the prescription for Percocet after having "Pharmacy C" void the electronic version.
d. Tell Mr. Smith he can only get the Percocet prescription at "Pharmacy C."

Mr. Smith can get his prescription filled at "Pharmacy A" only after the prescription at "Pharmacy C" has been voided. If Mr. Smith had already picked up his Percocet prescription at "Pharmacy A," the paper prescription should have been voided by the "Pharmacy C" pharmacist.

Schedule II substance regulations

Schedule II controlled substances require a written prescription that must be signed by the practitioner. There is no federal law stating when the prescription must be filled by after being signed by the practitioner. While some states and many insurance companies limit the quantity of controlled substances to a 30-day supply, there is no limit of quantities of drugs dispensed via a prescription. For Schedule II controlled substances, an oral order is only permitted in an emergency situation (DEA, 2012).

Schedule II refills

Prescriptions written for a Schedule II controlled substance may not be refilled (DEA, 2012).

Issuance of multiple prescriptions for Schedule II Substances

A practitioner may issue multiple prescriptions authorizing the patient to receive up to a 90-day supply of a Schedule II controlled substance provided the following conditions are met (DEA, 2012):

- Each separate prescription is issued for a legitimate medical purpose by an individual practitioner acting in the usual course of professional practice.
- The practitioner provides written instructions on each prescription indicating the earliest date on which a pharmacy may fill each prescription. The first prescription does not need a fill date on it if the prescriber intends for that prescription to be filled immediately.
- The practitioner concludes that providing the patient with multiple prescriptions in this manner does not create a risk of diversion or abuse.
- The issuance of multiple prescriptions is permissible under applicable state laws.
- The practitioner complies with all other requirements of the CSA and any other requirements of state law.

Facsimile and oral prescriptions for Schedule II Controlled Substances

A prescriber may transmit a Schedule II prescription to the pharmacy via facsimile to expedite the filing for the prescription. The original Schedule II prescription must be presented to the pharmacist for review prior to the actual dispensing of the controlled substance.

In an emergency, a practitioner may call in a prescription for a Schedule II controlled substance to the pharmacy. The pharmacist may dispense the prescription provided that the quantity prescribed and dispensed is limited to the amount adequate to treat the patient only during the emergency period. The prescribing practitioner must provide a written and signed prescription to the pharmacist within 7 days. The pharmacist must notify the DEA if the prescription is not received in that timeframe (DEA, 2012).

Exceptions to facsimile prescriptions for Schedule II Controlled Substances

The DEA has granted three exceptions to the facsimile prescription requirements for Schedule II controlled substances. The facsimile of a Schedule II prescription may serve as the original prescription as follows:

- A practitioner prescribing Schedule II controlled substances to be compounded for the direct administration to a patient by parenteral, intravenous, intramuscular, subcutaneous, or intraspinal infusion may transmit the prescription by facsimile.
- Practitioners prescribing Schedule II controlled substances for residents of long-term care facilities (LTCF) may transmit a prescription by facsimile to the dispensing pharmacy. The practitioner's agent may also transmit the prescription to the pharmacy.
- A practitioner prescribing a Schedule II narcotic controlled substance for a patient enrolled in a hospice care program certified and/or paid for by Medicare under Title XVIII or a hospice program that is licensed by the state may transmit a prescription to the dispensing pharmacy by facsimile. The practitioner or the practitioner's agent may transmit the prescription to the pharmacy and will note on the prescription that it is for a hospice patient (DEA, 2012).

Schedule III-V Substance regulations

A prescription for controlled substances in Schedules III, IV, and V issued by a practitioner, may be communicated either orally, in writing, or by facsimile to the pharmacist, and may be refilled if so authorized on the prescription or by call-in (DEA, 2012).

Refills

Schedules III and IV controlled substances may be refilled if authorized on the prescription. However, the prescription may only be refilled up to five times within 6 months after the date on which the prescription was issued. After five refills or 6 months, whichever occurs first, a new prescription is required (DEA, 2012).

Facsimile prescriptions for Schedules III-V substances

Prescriptions for Schedules III-V controlled substances may be transmitted by facsimile from the practitioner, or an employee or agent of the individual practitioner, to the dispensing pharmacy. The facsimile is considered to be equivalent to an original prescription (DEA, 2012).

Telephone authorization for Schedules III-V prescriptions

A pharmacist may dispense a controlled substance listed in Schedules III, IV, or V pursuant to an oral prescription made by an individual practitioner and promptly reduced to writing by the pharmacist containing all information required for a valid prescription, except for the signature of the practitioner (DEA, 2012). In the state of Florida, a pharmacist may not dispense more than a 30 day supply of a schedule III controlled substance upon an oral prescription (§893.04).

Verifying DEA numbers

In order to validate a prescription, the pharmacist should ensure that the prescriber has a legitimate DEA number. The pharmacist should double check the DEA manually and with their computer system.

The structure of a DEA number is 2 letters followed by 7 numbers (i.e. MD3221376):

1. First letter: Type of prescriber (A/B/F – Medical Doctor (MD), Doctor of Osteopathy (DO), Dentist, DVM (Doctor of Veterinary Medicine); M – midlevel practitioners (i.e. Nurse Practitioner (NP), Physician Assistant (PA), midwives).
2. Second letter: First letter of the practitioner's last name.

Formula to verify the DEA number (i.e. MD3221378):

1. Add the first, third, and fifth numbers (3+2+3 = 8).
2. Add the second, fourth, and sixth number (2+1+7=10).
3. Multiple the result of step #2 by 2 (2 x 10 = 20).
4. Add the result of step #1 to step #3 (8 + 20 = 28).
5. The last digit of this sum must be the same as the last digit of the DEA number (8).

Drug utilization review

A prospective drug utilization review involves evaluating a patient's planned drug therapy before a medication is dispensed. This process allows the pharmacist to identify and resolve issues before the patient actually receives the medication. Per Florida law, a pharmacist shall review the patient record and each new and refill prescription presented for dispensing in order to promote therapeutic appropriateness by identifying the following:

- Over or under utilization, including unusually high or low doses.
- Therapeutic duplication.
- Drug-disease contraindications.
- Drug-drug interactions.
- Incorrect drug dosage or duration of drug treatment.
- Drug-allergy interactions.
- Clinical abuse/misuse.
- Potential adverse reactions.

If a pharmacist recognizes any of these potential issues, the pharmacist shall take the appropriate steps to avoid or resolve the potential problem, including contacting the prescriber to discuss the issue and possible resolutions, as well as discussing drug utilization issues with the patient.

Corresponding responsibility

All pharmacists that fill prescriptions for controlled substances have a corresponding responsibility with the prescriber to ensure that the prescription is issued for a "legitimate medical purpose by an individual practitioner acting in the usual course of his professional practice." This means that the prescriber and the pharmacist both have a legal responsibility to ensure that the prescription is for a legitimate medical purpose. Per the DEA, pharmacists may not just fill the controlled substance without evaluating it for legitimacy. A pharmacist that fills a prescription not issued for a legitimate medical purpose or prescribed by a practioner not acting in the usual course of professional practice "shall be subject to penalties from a fine of $15,000 to 20 years imprisonment, or more if death or serious bodily injury occurs."

Pharmacists are expected to use their professional judgement when determine the legitimacy of a controlled substance prior to dispensing the medication. A pharmacist does not have to dispense a medication if the prescription is of doubtful, questionable, or suspicion origin (DEA, 2012).

Controlled substance security

The CSA requires pharmacies to have "effective controls and procedures to guard against the theft and diversion of controlled substances." This requirement ensures secures storage and distribution of controlled substances and limit drug diversion. Pharmacies can either store Schedule II-V controlled substances in a securely-locked, substantially constructed cabinet, or disperse throughout the stock of noncontrolled substances in a manner to obstruct the theft or diversion of the controlled substance (DEA, 2012).

Licensed practitioners who dispense controlled substances must store them in a securely locked, substantially constructed cabinet. Manufacturers, distributors, and narcotic treatment programs must store Schedule I and II substances in an electronically monitored safe, steel cabinet or vault (DEA, 2012).

The DEA must be notified of any theft or significant loss of controlled substances within one day of discovery (DEA, 2012). The Florida State Board of Pharmacy requires that the sheriff of the county be contacted within 24 hours of theft of controlled substances. The pharmacy shall also maintain a record which shall contain a detailed list of controlled substances lost, destroyed, or stolen, and the date of discovery. This record must be maintained for a minimum of 2 years for inspection and copying by law enforcement officials (§893.04).

DEFINITION OF CONTROLLED SUBSTANCE SCHEDULES

Schedule I controlled substances

The substances classified as Schedule I controlled substances have no accepted medical use in the United States. They have no accepted safe use under medical supervision and a high potential for abuse. Even though tetrahydrocannabinol (THC/marijuana) is legalized in some states for medical and recreational use, it is still a Schedule I substance.

Examples of Schedule I controlled substances: heroin, marijuana (cannabis), lysergic acid diethylamide (LSD).

Schedule II controlled substances

Substances with an accepted medical use and high potential for abuse are classified as Schedule II controlled substances.

Examples of Schedule II:	
Generic	**Brand**
Amphetamine	Adderall
Codeine	
Fentanyl	Abstral, Actiq, Duragesic, Fentora, Lazanda, Onsolis, Sublimaze, Subsys
Hydrocodone	
Lisdexamfetamine	Vyvanse
Meperidine	Demerol
Methadone	Dolophine, Methadose
Methylphenidate	Concerta, Daytrana, Metadate CD, Metadate ER, Methylin, Quilivant XR, Ritalin
Morphine	MS IR, MS Contin, Roxanol
Oxycodone	Endocet, OxyContin, OxyIR, Percocet, Roxicodone, Roxicet
Oxymorphone	Opana, Opana ER
Remifentanil	Ultiva
Sufentanil	Sufenta

Schedule III Controlled Substances

Substances in this schedule have an acceptable medical use and less of a potential for abuse than in Schedules I or II substances. Abuse of Schedule III narcotics may lead to moderate physical dependence or high psychological dependence.

Examples of Schedule III narcotics	
Generic	**Brand**
Buprenorphine	Butrans, Suboxone
Butalbital	Fiorinal
Codeine combination products with < 90 mg/dose	Tylenol #2, #3, or #4
Ketamine	Ketalar
Testosterone	Androderm, AndroGel, Depotest

Schedule IV controlled substances

The substances classified as Schedule IV controlled substances have a low potential for abuse compared to Schedule III controlled substances.

Examples of Schedule IV controlled substances	
Generic	**Brand**
Alprazolam	Xanax
Armodafinil	Nuvigil
Carisoprodol	Soma
Clonazepam	Klonopin
Clorazepate	Tranxene
Diazapem	Valium
Eszopiclone	Lunesta
Lorazepam	Ativan
Midazolam	Versed
Modafinil	Provigil
Phentermine	Adipex-P
Temazepam	Restoril
Triazolam	Halcion
Zaleplon	Sonata
Zolpidem	Ambien, Edluar, Intermezzo, Zolpimist

Schedule V controlled substances

Substances classified as Schedule V controlled substances have a low potential for abuse relative to Schedule IV controlled substances. This schedule primarily consists of medications containing limited quantities of certain narcotics.

Examples of Schedule V substances	
Generic	**Brand**
Codeine preparations 200mg/100mL	Robitussin AC
Diphenoxylate preparations	Lomotil
Lacosamide	Vimpat
Opium preparations 100mg/100mL	
Pregabalin	Lyrica

Florida legal cases

As a result of the increases in opioid-related deaths, the Drug Enforcement Agency (DEA) has become much more aggressive in its enforcement of the Controlled Substances Act. The DEA has ramped up its activity in Florida, due to its high overdose rate and pill mill production.

In 2015, the DEA cracked down on pill mills in Florida. Prescription drug addicts were traveling to Florida to access physicians that were prescribing pain medications without a legitimate medical reason and pharmacies were filling them despite warning flags. CVS acknowledged that its retail pharmacists had a "responsibility to dispense only those prescriptions that were issued based on a legitimate medical need." They also acknowledged that their pharmacists did not comply with the Controlled Substances Act. CVS paid a $22 million dollar fine to the United States for unlawful distribution of controlled substances (Department of Justice, 2015).

In 2016, a pharmacist was sentenced to more than 24 years in federal prison for distributing and dispensing oxycodone without a legitimate medical purpose. The pharmacist, Valentine Okonkwo, dispensed more than 500,000 oxycodone pills and collected more than $1.3 million from illegal sales. The pharmacist accepted fraudulent prescriptions from patients who travelled long distances, in groups, and paid cash (Department of Justice, 2016).

Case study

Mr. Thomas is a long-standing patient at your pharmacy. Recently, he has been diagnosed with osteoarthritis and referred to a pain management physician. He is a 49-year-old male, recently divorced, with a steady job and commercial insurance. He is a reformed heroin abuser and smokes one pack of cigarettes per day. His other medical problems include asthma (albuterol), hypertension (lisinopril), and hyperlipidemia (atorvastatin). He brings you a prescription for Oxycontin and Oxycodone IR from a local pain management physician.

When reviewing the prescription, what are some items that help validate that this prescription is legitimate?

- Known patient to the pharmacy.
- Local pain management prescription.
- Utilizing commercial insurance.

What are some factors that put Mr. Thomas at a higher risk for opioid overdose?

- Asthma.
- Former drug abuser.

What are some counseling points you should discuss with Mr. Thomas?

- Utilizing medications as prescribed by physician.
- Trying alternate non-opioid medications.
- Keeping medications secured.
- Keeping follow-up appointments with physician to evaluate efficacy.

Conclusion

Pharmacists play a key role in protecting controlled substances from diversion. They can help keep the public safe and prevent overdoses by utilizing pharmacy law and good sound judgment. Pharmacists should make sure the controlled substances will be used for a valid legitimate medical purpose by utilizing prescription drug monitoring programs, "red flags," and communication with the prescriber.

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Final Examination Questions

Select the best answer for each question and then proceed to **EliteLearning.com/Book** to complete your final examination.

6. When a pharmacist detects that a prescription is invalid, which of the following is considered a minimum standard to be used before refusing to fill the prescription?
   a. Communicate with the prescriber.
   b. Communicate with the patient or patient's representative.
   c. Access E-FORSCE.
   d. All of the above.

7. How many times may a pharmacist refill a prescription for hydrocodone?
   a. 0.
   b. 1.
   c. 6.
   d. 12.

8. Which of the following is a valid DEA number for Dr. Billings?
   a. AB5634120.
   b. BB9081247.
   c. BB1325403.
   d. AC3284442.

9. How many morphine mg equivalents per day is a prescription for Oxycodone CR 60mg PO BID?
   a. 60mg.
   b. 90mg.
   c. 120mg.
   d. 180mg.

10. Which of the following is required for a pharmacist to dispense naloxone?
    a. A valid prescription from a physician.
    b. A properly labeled naloxone medication.
    c. An order from any licensed prescriber.
    d. Insurance authorization.

11. Which patient at high risk for overdose?
    a. A patient with sleep apnea.
    b. A 75 year old patient.
    c. A patient with history of substance abuse.
    d. All of the above.

12. Which of the following does not need to be on a controlled substance prescription?
    a. Patient's name.
    b. Patient's address.
    c. Patient's phone number.
    d. Prescriber's DEA

13. How many days' supply of oxycodone can a Florida Physician Assistant write for?
    a. 0.
    b. 7.
    c. 30.
    d. Unlimited.

14. What dose of Morphine milligram equivalent (MME) increases risk of overdose without increasing pain control?
    a. > 10 MME.
    b. > 20 MME.
    c. > 30 MME.
    d. > 50 MME

15. Which of the following does not need to be submitted to E-FORCSE?
    a. Oxycodone administered to a nursing home patient.
    b. Hydrocodone dispensed in an outpatient pharmacy.
    c. Acetaminophen with codeine dispensed in a retail pharmacy.
    d. Morphine dispensed at a specialty outpatient pharmacy.

16. What is the redirection of a prescription drug from its lawful purpose to an illicit use?
    a. Misuse.
    b. Abuse.
    c. Diversion.
    d. Addiction.

17. Who does a pharmacist have to report a suspected diverting prescriber to?
    a. Department of Health.
    b. State Board of Pharmacy.
    c. Homeland Security.
    d. Prescriber's employer.

18. A prescriber calls in a prescription for Fiorinal to a pharmacy. What is the maximum days' supply that can be dispensed?
    a. 7.
    b. 14.
    c. 30.
    d. 60.

19. Which of the following are red flags for a pharmacist?
    a. A known patient to the pharmacy.
    b. A prescription written for a 7 day supply of opioid medication.
    c. A prescription from a prescriber located 3 hours away.
    d. A new prescription from a pain management physician.

20. What schedule of controlled substance is available on the E-FORCSE report?
    a. II.
    b. II, III.
    c. II, III, IV.
    d. II, III, IV, V.

Course Code: RPFL02VC

Chapter 3: Medicinal Marijuana

5 Contact Hours

By: Martha Mathews Libster, PhD, MSN, APRN-CNS, APHN-BC

Author Disclosure: Martha Mathews Libster and Colibri Healthcare, LLC do not have any actual or potential conflicts of interest in relation to this lesson.

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Learning objectives

After completing this course, the learner will be able to:

- Distinguish medicinal marijuana (Cannabis sativa) from recreational marijuana and the use of hemp.
- Discuss the state of pharmaceutical drug development from the marijuana plant and its potential applications in nursing care, behavioral health, and medical treatment.
- Summarize the state of the science concerning the best clinical research evidence for use of marijuana in the treatment of disease, including supportive and complementary care.
- Identify the current status of legalization of marijuana for medicinal and recreational use and its impact on healthcare systems.
- Review the emerging issues for community health and education related to marijuana use and the expansion of legalization/decriminalization for medicinal and recreational purposes.

Introduction

Throughout history, plants have occupied central roles in health beliefs and practices, healthcare systems, sociopolitical controversy, and healthcare reform. In the 19th century, lobelia (Lobelia inflata), a plant indigenous to the North American continent and used medicinally for centuries by indigenous peoples, gained attention. The plant was used both to aid respiration and to induce vomiting for various health and spiritual concerns (Moerman, 1998). Lobelia became the focus of health care during a period of extensive healthcare reform (Berman & Flannery, 2001). There was debate about the safety of lobelia just as there is today with other controversial plants in commerce, such as ephedra (Ephedra sinensis), tobacco (Nicotiana tabacum), and marijuana (Cannabis spp.). Medicinal use of plants continues to be one of the cornerstones of healthcare cultures and systems around the world. Because of their accessibility, cultural history, and relatively safe record of traditional use, medicinal plants remain at the center of health care as traditional medicine (World Health Organization, 2013). Over the years, leading plant scientists such as Farnsworth and Soejarto (1991) reported the existence of more than 250,000 higher species of chemically distinct plants on Earth, of which between 35,000 and 70,000 have been used medicinally over the centuries. It is estimated that only a fraction of all flower-bearing plants have been examined and only a small subset has had their chemical constituents identified or had their healing properties researched in double-blind, placebo-controlled trials. The potential of the plant world for producing cures for disease and relief from everyday discomfort is recognized by botanists, ethnobotanists, and pharmacognosists (people who pursue drug discovery from plants). The public continues to be a driving force in medicinal plant use. People follow their time-honored plant-oriented healing traditions in self-care practices. They also urge the scientific community to develop new drugs and applications. All healthcare paradigms – self-care, traditional medicine, and biomedical – are represented in this course on the medicinal use of marijuana. This plant, which has been employed for centuries in self-care and traditional medicine, is now the focus of much interest in terms of biomedical development for use in alleviating diseases and in chronic pain management. Yet, as will be discussed in this course, marijuana is federally classified as illegal.

This course is an introduction to the genus Cannabis (and species such as sativa and indica). It presents a synopsis of the plant's history and the state of the science that can be used to better understand, interpret, and then inform public and professional exploration, from self-care to traditional use to biomedicine and clinical trials. This course also reviews some of the debate regarding the potential social implications for community health related to the increasing alignment of economies, state-by-state, with the promotion of marijuana cultivation, product development, and use for recreational and medicinal purposes.

A review of the literature produces thousands of reports, theoretical and population research papers, and books, on medicinal marijuana. Far fewer clinical trials exist, however, that might begin to answer some of the questions from the public and health professionals about the physical and psychological effects of the plant and its constituents. This course offers a synopsis of traditional and biomedical data about the plant and the issues related to public and professional use in an attempt to answer some of the most common questions that professionals in nursing, behavioral health, and pharmacy may have when counseling those who are deciding whether to choose marijuana. As this course will show, the breadth of marijuana information and research in some areas is stunning. Depth of exploration is less so. Public and professional concerns about the psychoactive nature of Cannabis vary. Marijuana, for both medicinal and recreational use, is a highly controversial and disputed subject. It is important to note that it is not the purpose of this course to sway opinion for or against marijuana. The teacher/author of this course has done her best to present information, data,

and resources, as well as trends in the professional literature in pharmacy, medicine, nursing, and behavioral health, that can inform decision making. Person-centered care is the stated goal of individuals committed to healthcare reform. This course does suggest that, given the exponential growth in interest, marijuana use for recreational as well as medicinal purposes be included in health professionals' assessments, as are alcohol and tobacco, two other plant-based public health concerns. This course prepares healthcare professionals to address recreational marijuana use with each person in their care and to make informed choices when marijuana is considered for medicinal use in care, comfort, or disease management.

Although healthcare professionals and leadership, including those at the National Institutes of Health (National Academies of Science, Engineering, and Medicine, 2017) and the World Health Organization (2013), call for such research, the federal prohibition on marijuana in the United States creates a challenge for science that involves an illicit drug. Public attraction to marijuana for health and recreation helps drive medical science to delve further into exploration of the emerging evidence of the role of the endocannabinoid system in health and disease. Establishment of a body of clinical-trial research science on marijuana to complement current evidence might better inform the public's health decision making and best-practice guidelines for healthcare professionals. However, as will be demonstrated in this course, even if federal laws were to loosen or be abolished, feasibility would be a big hurdle. This course includes references to the most current research evidence available, drawing, when possible, on clinical trial research.

There is much to learn, however, about medicinal marijuana from evidence other than clinical trials. This course includes historical data and evidence from in vitro studies, literature reviews, meta-analyses, surveys, and community health studies that have contributed in a meaningful way to current scientific understanding of the health outcomes witnessed in the public sphere, where marijuana use is proliferating.

Botanical Clarification: This course adopts the common name "marijuana" to refer to the species Cannabis sativa and C. indica, as well as hybrids of the two. The science of botanical nomenclature requires that a genus and species name be italicized and that the genus be capitalized. Much of the medical and scientific literature refers to marijuana as "cannabis" not Cannabis spp., and state registries use the term "marijuana," not Cannabis. Marijuana is the term commonly employed by the public. Although supporters of marijuana use and legalization are concerned about the social stigma surrounding the use of the word "marijuana," there is no intention to further stigmatize the plant in this course. The common name for the plant was chosen for the title of this course because it is likely to be more recognizable by health professionals seeking continuing education courses that include the information provided here. For consistency, ease, and clarity, the term "marijuana" will be used. Botanical names may also be employed to add specificity to the information presented.

Disclaimer: Throughout history, plants have been at the center of controversies about health care. Marijuana (Cannabis spp.) is one of those plants. Medicinal marijuana is a highly controversial topic in the United States today. The act of authoring this course should not be misconstrued as agreement with or opposition to the use of marijuana, recreationally or medicinally, or alignment with the movement to legalize marijuana. The author has done her job as an educator, clinical herbalist, and historian-scientist. She has made every effort to offer the nurses, pharmacists, and behavioral health professionals who participate in the course a balanced review of the state of the science of marijuana's application in health care within the context of history and tradition so that they may be better informed. Most importantly, the author has attempted to present an understanding of the plant at the center of the sociocultural and political debate and to provide explanation and analysis of the possible meaning of the plant's dominance at this time.

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CHAPTER 1: BOTANICAL BACKGROUND, CULTURAL HISTORY, AND MISUSE OF MARIJUANA (CANNABIS SPP.)

A person who walks across a lawn, cultivates a garden, or forages in forests and water is engaging with the plant world of trees, flowers, grasses, fungi, fruits, food, and medicinal plants. Although marijuana (*Cannabis spp.*) is but one of thousands of types of plants, it is a common topic of private and public conversations in the early 21st century. Furthermore, marijuana is perhaps one of the most praised and condemned plants in history. This chapter explores the medicinal qualities of marijuana and its constituents, as well as the cultural history that continues to grow with the plant and its role in forming U.S. drug enforcement policy. The chapter also introduces some of the suggested reasons for the resurgence of interest in marijuana among Americans seeking healing, relief, and hope and the reversal from many in the public from demanding prohibition to lobbying for legalization (McKenna, 1992). Healthcare professionals who are engaged in shared decision making with people in their care can employ the context provided by cultural history, including botanical science and clinical trial data. Marijuana's history in treating various conditions is long and successful. It is not the newest drug on the market, though new drugs have been manufactured from its constituents. Marijuana contains chemical compounds and nutrients that can affect changes in people's physical, emotional, mental, and spiritual health and well-being. Whole marijuana leaf or seed is what people commonly use. Marijuana has retained its culture of traditional use referred to by scientists as "crude" medicine – when a plant is used in a form close to its natural state. Some might think of the term "crude medicine" as suggesting that the medicine is simple, but medicinal plants, including marijuana, are rarely simple. When studied more closely, they reveal themselves to be replete with hundreds of chemical constituents, many of which can make powerful biochemical changes. Although this course does include some of the important specific botanical and pharmaceutical data and known mechanisms of action of marijuana (see Chapter 2), the evidence of human use gleaned from cultural history in this chapter, as well as the course in general, will provide the healthcare professional with a foundation for insight into care for those either considering the use of marijuana or already using it.

Even people who have no knowledge of the newest drug on the market for pain or disease probably grew up knowing about marijuana just as they might know about tobacco (*Nicotiana tabacum*) and the alcoholic beverages that are made from numerous plants. People who are using marijuana have a story to tell their nurse, pharmacist, or behavioral health practitioner. The first step in the care of the person using marijuana is to gather that story, which is the natural history of his or her use. Because marijuana has a large variety of applications, this chapter provides the first information a healthcare professional needs when caring for the user: knowledge about the plant and its traditional use.

Marijuana has four basic uses, as food, fiber, recreation, and medicine. It can also be used in excess, resulting in substance abuse. However, the boundaries between the various uses can be blurred. It is not always easy, for example, to distinguish recreational and medicinal use of whole marijuana leaf or seed. The difference may be determined best by the intention and practice of the user. Terence McKenna (1992, p. 163) suggests that the employment of the term "recreational" when applied to substance use "trivializes the cognitive impact of the substance used," and that "low doses of most drugs that affect the central nervous system are felt by the organism as artificial stimulation or energy, which can be directed outward in the form of physical activity in order both to express the energy and to quench it." However, "recreational use" is still a term used globally to describe the purpose of becoming intoxicated (using marijuana to "get high") for personal amusement rather than for a health concern. People often choose to self-prescribe marijuana for recreational use. But people also consciously self-care or self-medicate with marijuana. There is an entire subculture today that promotes daily self-medication with marijuana (usually through smoking), just as there was a hashish-eating culture before the 19th century. Some people perceive marijuana as a contributor to human society's evolution to greater peace and tolerance. Two of the authors who have been recognized as providing some of the best insights into marijuana's history of use are ethno-botanist Terence McKenna and author Martin Lee, 1994 winner of the Pope Foundation Award for Investigative Journalism. McKenna, renowned for his work on plant hallucinogens, writes of marijuana in his book *Food of the Gods* (1992) that, although people tend to focus on episodes of intoxication when talking about plants/drugs like marijuana, individuals regularly use plants like marijuana – as well as other less intoxicating plants such as coffee (*Coffea arabica*) and tea (*Camellia sinensis*) – that best ensure a response such as energy stimulation, relaxation, or mood elevation. When healthcare professionals ask about their self-medication patterns of use with tobacco, alcohol, and caffeine, people may reveal a regular history of use. McKenna writes that, "Plant use is an example of a complex language of chemical and social interactions. Yet most of us are unaware of the effects of plants on ourselves and our reality, partly because we have forgotten that plants have always mediated the human cultural relationship to the world at large" (1992, p. 15). Marijuana use can thus be seen as yet another mediator of that relationship. Marijuana users have *not* forgotten the time-honored relationship with medicinal plants; they actively and consciously engage in it. Some even capitalize on it.

Healthcare professionals, who prescribe drugs or herbs in their practices, may advise and prescribe marijuana for medicinal purposes in states where it is legal to do so and warranted in care (Chapter 4). Martin Lee, in his 2012 book *Smoke Signals,* writes that in the 19th century it was common physician practice to prescribe marijuana. The toxicology of a plant, as well as its history of safe use in a particular manner, is a consideration in risk-benefit shared decision making. Toxicology is determined not only by the constituents in a plant but also by the responses of the humans who use the plant. Healthcare professionals are challenged to understand the health behaviors of people engaged in plant use, especially when the healthcare professional has not experienced use of the plant. Because marijuana is currently an illegal substance under federal law, many healthcare professionals may not have firsthand experience with the effects of marijuana. Psychoactive plants such as marijuana, along with the user's quest for an altered state of consciousness and possible involvement in a lifestyle that includes daily use, pose unique challenges to healthcare professionals. The healthcare issues are complex, as some users, by the very nature of their choice to use marijuana, challenge society's "modern idea of the ego and its inviolability and control structures … throwing into question the entire world view of the dominator culture" (McKenna, 1992, p. xx).

As each state re-examines the legal status of marijuana, healthcare professionals may be compelled to re-examine marijuana and their own roles in supporting use in self-care and professional health care. This re-examination does not necessarily mean that healthcare providers will change their opinions. However, reflection is a natural response to mounting public inquiry of health professionals as the industry grows exponentially. Contemporary beliefs about marijuana run the gamut from prohibition to social promotion. Some consider marijuana, when compared with alcohol, to be "benign." Others are concerned that marijuana may serve as a "gateway" drug. Still others ask why people seek the escape of a "high" in the first place. The existential issues of substance use and misuse are just as important with marijuana as with any other drug. Although concerns over marijuana's use, misuse, and global market may have been to a certain degree eclipsed by the current focus on the "opioid crisis," its impact continues to be reported by the U.S. National Institute on Drug Abuse and the United Nations Office on Drugs and Crime (UNODC) that concludes the following:

> *Research has shown that, notwithstanding the usefulness of some cannabinoids in the management of specific medical conditions, their use, particularly in the botanical form of herbal cannabis with unknown content and dosage, can be detrimental to health. To protect human health, it is therefore necessary that the principles of safety, quality and efficacy and the rigorous scientific testing and regulatory systems that apply to established medicines be applied also to cannabis-based medicines* (UNODC, 2017b, p. 29).

The National Center for Complementary and Integrative Health (NCCIH) currently disputes the beneficial use of marijuana, stating that:

> *The U.S. Food and Drug Administration (FDA) hasn't found that marijuana is safe or effective for treating any health problems. However, some states and the District of Columbia allow its use for certain health purposes. States have legalized medical marijuana because of decisions made by voters or legislators – not because of scientific evidence of its benefits and risks* (NCCIH, 2017).

The NIDA website states that, currently, the quality of health research on marijuana and its components varies widely, with exception of the research done on two FDA-approved medications, dronabinol and nabilone approved to treat chemotherapy-induced nausea and vomiting (See Chapter 2). Marijuana whole plant is "significantly more potent now and we now know a lot more about the potential harmful effects of marijuana on the developing brain." brain" (National Institute on Drug Abuse [NIDA], 2016).

Although some may view the subject of marijuana as "increasingly difficult to talk about – in part because of the mixed messages being sent by the passage of medical marijuana laws and legalization of marijuana in some states" (NIDA, 2017c), health professionals can choose to become informed so that they can play a discerning role in the current dialogue about what is best for the people in their communities and states. In support of that role, this course presents cultural and historical context for the use of marijuana over the centuries with the evidence from the best clinical research available, including data from botanical science and clinical trials. It is the botanical background that may explain what might have attracted people to marijuana for thousands of years.

BOTANICAL BACKGROUND

Marijuana (*Cannabis spp.*) is a strong plant with stems that grow easily from 3 to 20 feet in nearly every climatic condition. The leaves are palmate (they look like the palm of a human hand), each with five to seven lanceolate (long and pointed) leaflets. The plant is native to Northern India and Southern Siberia and is a member of the small Cannabaceae family of plants. One other medicinal plant in the Cannabaceae family is hops (*Humulus lupulus*), a plant employed in the brewing of beer. Carl Linnaeus, the 18th century Swedish botanist and physician who created a system for naming plants (The Linnean Society, 2018), named marijuana *Cannabis sativa* in 1753. Marijuana that is cultivated in a dry, hot climate, produces resin in greater quantities along with fiber that is poor for commercial purposes. In countries with milder, humid weather the hemp fiber is stronger and more durable and less resin is produced (Abel, 1980). Because of the historical emphasis on hemp cultivation for quality fiber, the intoxicating effects of marijuana were largely unknown in America until the 19th century. Today, however, the leaves, seeds, flowers, and stems, along with the resin that oozes from the stems and leaves of the plant, are used medicinally, recreationally, and in ritual. (See Table 1-1.) When marijuana is harvested for fiber or its leaf, it is cut close to the ground with a special sickle. Harvesting resin is more painstaking. The resin is known as "hashish." *Cannabis indica* is the species typically grown for its higher resin content for the hashish market. A late 19th-century analysis described the leaves as containing chlorophyll, a volatile oil, gummy extractive, a bitter body, albumen, lignin, sugar, and salts such as potassium nitrate, silica, and phosphates (Felter & Lloyd, 1898/1983). Approximately 60 cannabinoids (plant constituents discussed in detail in Chapter 2) have been identified in marijuana, but delta-9-tetrahydrocannabinol, or "THC," is the main psychoactive component.

Smoking marijuana has a paradoxical effect on mood: It can be stimulating or sedating. This type of effect is not typical of central nervous system stimulants or depressants, but it is more consistent with the effects of psychedelic drugs such as lysergic acid diethylamide (LSD; Block, Erwin, Farinpour, & Braverman, 1998). Marijuana plants are dioecious, which means that there are distinctly male and female plants. Growers focus on the identification, care, and propagation of female plants because females produce more resin and flower later (Abel, 1980). "Not only do males not produce a usable drug, but if pollen from male plants reaches females, the females will begin to 'set' seed and will cease their production of resin" (McKenna, 1992, p. 154). The intoxicating resin is secreted by glandular hairs located around the flowers.

Table 1-1: Marijuana Plant Preparations

Preparations	Description
Marijuana*	Dried plant product consisting of leaves, stems, and flowers; typically smoked as a rolled cigarette or vaporized.
Hashish	Concentrated plant resin often cooked into pastry such as cake that can be ingested; also can be smoked.
Hashish oil	Oil obtained from the cannabis plant by solvent extraction; usually smoked or inhaled; butane hash oil (sometimes referred to as "dabs").
Alcohol extract/Tincture*	Cannabinoid liquid extracted from the plant; consumed sublingually.
Oil infusion*	Plant material mixed with nonvolatile solvents such as butter or cooking oil and ingested.

*These preparations are available from state-approved medical marijuana dispensaries. *Note.* From Western Schools, © 2018.

Is there a difference between marijuana and hemp?

Marijuana is the most used common name for *Cannabis sativa* in the West; however, there are numerous others. As Terence McKenna (1992, p. 150) comments, "The thousands of names by which cannabis is known in hundreds of languages are testament to its cultural history and ubiquity." There is a significant difference, however, between plants known by the common names "marijuana" and "hemp." Although they are both *Cannabis sativa,* hemp is a different strain of marijuana that is low in THC. Marijuana (and hemp) seeds contain no THC, and can thus be sold in the market as food; but during processing it is possible for trace amounts of THC from the leaf to stick to the outer husk of the seed in an amount that is measurable upon analysis. Hemp products on the market cannot have THC. Hemp seed, which is used in producing soap, lamp oil, and paint as well as food products such as oil and butter, is 31% protein after the husk is removed. It is rich in vitamins, minerals, and nutrients, such as linoleic acid (an essential fatty acid) and tocopherols (vitamin E), and the concentration of unsaturated fatty acids can exceed 90%, higher than most vegetable oils on the market, particularly the Yunma No. 1 and Bama Huoma varieties (Chen et al., 2010). Hemp seed oil is high in flavonoids, such as flavanones, flavanols, and isoflavones, which are known antioxidants (Smeriglio et al., 2016).

A common recipe for the use of hemp seed is hemp porridge. The hemp plant is best known, however, for its use in fiber production, primarily of cordage for weaving and rope making. Hemp fiber, along with mulberry tree bark pulverized into pulp, was also the basis for the invention of paper traditionally ascribed to a Chinese court official, Ts'ai Lun, in AD 105. However, fragments of paper containing hemp fiber have been found in Chinese graves dating back to the first century BC (Abel, 1980).

Ritual use of marijuana

Marijuana has a rich history that spans the gamut from high social acclaim as a plant of great spiritual power to intense suspicion. The plant has been associated with ritual, religious, social, and medical customs in India for thousands of years. Marijuana is referred to as one of the five sacred plants suggested for freedom from anxiety in the *Atharva Veda* (circa 1400 BC), an ancient Indian text on healing (Abel, 1980). In Tibetan tantric tradition, marijuana is burned to drive out evil forces. Gautama Buddha is said to have subsisted on one hemp seed each day for 6 years preceding his enlightenment. Alternatively, the term "assassin" used in the English language is thought to have been derived from the word *hashishin,* which was applied to a murderous sect, which in its religious rites, used hashish for intoxication (Felter & Lloyd, 1898/1983). One of the few surviving books of the *Zend-Avesta,* ancient holy book of the Zoroastrians, *Vendidad,* translated as the "Law Against Demons," calls *bhanga* a "good narcotic" that may allow some of the highest mysteries to be revealed. Chinese priest-doctors used marijuana stalks engraved with snake-like figures in their demon-ridding rites (Abel, 1980). There also is reference to marijuana in the *Talmud,* a holy book in Jewish culture. Marijuana is referred to in Mexico as "*mota.*" The Mexican phrase "*esta ya le dio las tres,*" or "you take three times (puffs)" of marijuana, refers to mota as the "opium of the poor" used as a hangover-free intoxicant, a "social lubricant and an antidote to drudgery and fatigue" (Lee, 2012, p. 39).

Marijuana leaf, or resin from the leaf and stem (hashish), is typically smoked. The resin and seed of the plant can also be eaten. Eating hashish was the preferred method of ingestion for centuries. Smoking of *Cannabis* was introduced to Europe only after Columbus returned with tobacco from his second trip to the New World (McKenna, 1992). Traditionally, the effects of smoking are thought to be more immediate. A variety of apparatuses and techniques are available for smoking marijuana. The favorite device for smoking marijuana in India is a *chelum,* a wooden, ceramic, or soapstone tube that is packed with herb. The Scythians, a nomadic Central Asian people, are credited with bringing marijuana to Eastern Europe around 700 BC (McKenna, 1992) and discovering that inhalation was the most effective way to appreciate the effects of the plant. Centuries later, Dr. William B. O'Shaughnessy, scientist and physician, is said to have introduced marijuana to England in 1842 in his *Bengal Dispensatory and Pharmacopoeia* (Block et al., 1998).

Marijuana seed has been used in traditional Chinese medicine. The ancient emperor Shen Nung (circa 2700 BC), patron of agriculture, is credited with the discovery of marijuana as a medicine. Marijuana seed, or "*huo ma ren,*" is classified as "moist laxative" in the Chinese *Materia Medica* (Bensky & Gamble, 1993). It is also used in patterns of yin (heat) deficiency with constipation, such as may occur in older adults after illness with fever and in women postpartum. Poultices of the pounded seed are used on wounds to clear the heat in the wound and promote healing. The ground seed is also known to be effective in lowering blood pressure in animals and humans (Bensky & Gamble, 1993) It is typically used with other herbs in formulation. The Chinese have historically used marijuana with wine to create an anesthetic called *ma-yo* when performing difficult surgical operations. According to Abel (1980), "The Chinese were well aware of marijuana's unusual properties … many did not approve. Due to the growing spirit of Taoism which began to permeate China around 600 BC, marijuana intoxication was viewed with special disdain" (p. 13). By the first century of the Common Era, the Taoists had relented and, going along with their interest in magic and "seeing spirits," people were once again adding marijuana seeds to their incense burners.

The Ohio State Medical Society conducted the first official U.S. government study of marijuana in 1860. They catalogued conditions that doctors had successfully treated with marijuana, from "bronchitis and rheumatism, to venereal disease and post-partum depression. The use of marijuana as an analgesic was so common that medical textbooks and journals identified several types of pain for which it should be administered" (Lee, 2012, p. 26). In Great Britain, "Sir William Osler, often called the founder of modern medicine, endorsed marijuana as the best treatment for migraine headaches" and Sir John Russell Reynolds, the personal physician to Britain's Queen Victoria, prescribed hemp to the queen to relieve her menstrual cramps, calling it "one of the most valuable medicines we possess" (Lee, 2012, p. 26). Marijuana was used for such conditions as:

> *Delirium tremens, neuralgia, gout, rheumatism, infantile convulsions, low mental conditions, insanity, etc., and in inflammatory conditions in cases where opium disagrees and is often preferable to opium. Acute mania and dementia, epilepsy … are among the nervous disorders in which it exerts a positively beneficial and soothing action … The drug is a useful hypnotic for the insane. As a remedy for pain, it ranks among the first; the more spasmodic the pain the better it acts* (Felter & Lloyd, 1898/1983, p. 425).

An alcohol tincture of marijuana leaf in sweetened water has been used medicinally to increase the strength of uterine contractions without adverse effects, as well as for menorrhagia and chronic cystitis. Herbalists use marijuana tincture in combination with lady's mantle (*Alchemilla vulgaris*) and witch hazel (*Hamamelis virginiana*) to slow postpartum hemorrhage caused by uterine atrophy (Weed, 1986). "Impotence is said to have been cured by it. Cannabis has some reputation as a remedy for chronic alcoholism, and for the cure of the opium habit" (Felter & Lloyd, 1898/1983, p. 426). The Iroquois have used marijuana as a psychological aid for people who are recovering from illness but somehow do not think that they are getting well (Moerman, 1998).

In Ayurveda, a traditional medicine of India, marijuana is referred to as *vijaya, siddhapatri, ganjika, bhanga,* and *hursini* (Nadkarni, 1976). Bhang was a symbol of hospitality and given to guests. Sushruta, a renowned physician of ancient India, recommended marijuana to relieve congestion and regulate body fluids, and as a sleep and digestive aid, analgesic, and aphrodisiac. At the start of the 18th century, Gobind Singh, the Tenth Guru of the Sikh religion, gave bhang to soldiers facing life-threatening missions (Abel, 1980). In Ayurveda, marijuana has been used in treating numerous infectious diseases (Touw, 1981). Some Indians regard marijuana as "*sattvik nasha*" or "peaceful intoxication." To make *thandi,* an intoxicating drink whose effect lasts 3 hours without hangover, marijuana powder is mixed with equal parts black pepper, dried rose petals, poppy seeds, almonds, cardamom, cucumber and melon seeds, sugar, milk, and water (Nadkarni, 1976).

The marijuana "high"

The marijuana "high," or intoxication, is described in different ways. Some people report feeling inebriated, while others are simply relaxed. Some people use plants such as marijuana in the pursuit of religious, spiritual, or ecstatic experience. Humans tend to be fascinated with altered states of consciousness, be it through prayer, meditation, music and the arts, drugs, or plants. Traditional shamans regard plants as more than sources of foods and drugs, seeing them as sentient life forms that are interdependent and communicate with each other and humans. Tompkins and Bird (1973), in their classic book *The Secret Life of Plants,* conducted clinical research on the spiritual as well as physical and emotional relationships between plants and people. McKenna (1992, p. xvii) states that:

> *Analysis of the existential incompleteness within us that drives us to form relationships of dependency and addiction with plants as drugs will show that at the dawn of history, we lost something precious, the absence of which has made us ill with narcissism. Only a recovery of the relationship that we evolved with nature through use of psychoactive plants before the fall into history can offer us hope of a humane and open-ended future.*

Nineteenth-century Americans and Europeans preferred to ingest marijuana baked into pastry or as a tincture in tea or wine, until people began to realize that they could achieve a milder, quicker, and more manageable high by inhaling marijuana fumes. Smoking hashish was considered at the end of the 19th century to be "stylish and elegant" (Lee, 2012, p. 37). Adolescents and young children are smoking marijuana to get high too. The NIDA (2017b) public education materials list the following signs and symptoms of the marijuana high in youth:

- Chronic cough.
- Unusually giggly and/or uncoordinated.
- Very red, bloodshot eyes or use eyedrops often.
- Hard time remembering things that just happened.
- Has drugs or drug paraphernalia – drug-related items including pipes and rolling papers – possibly claiming they belong to a friend if confronted.
- Has strangely smelling clothes or bedroom.
- Uses incense and other deodorizers.
- Wears clothing or jewelry or have posters that promote drug use.
- Has unexplained lack of money or extra cash on hand.

The scientific explanation for the high from smoking marijuana is that when a person inhales, the THC (see Chapter 2) in the leaf is released into the lungs, where it passes into the blood. The amount of THC consumed determines the potency effects, ranging from sedating to psychoactive. The effects of smoking are rapid, whereas the effects from eating marijuana or hashish can be delayed by at least 30 to 60 minutes. The THC acts on brain receptors (to be discussed further in Chapter 2) that also receive chemicals involved in normal brain function and development. According to NIDA (2017c), science suggests that "marijuana overactivates parts of the brain that contain the highest numbers of these receptors causing the 'high' that people feel." People also feel other effects from marijuana, such as changes in mood, impaired movement, altered sense of time, sensory alterations, difficulty thinking and problem solving, and impaired memory (NIDA, 2017c). Chronic users of marijuana can generally distinguish between the highs produced by smoking *Cannabis sativa* versus the effects of *C. indica.* The *C. sativa* high is characterized as uplifting and energetic, felt in the head and described as spacey or hallucinogenic. *C. sativa* gives a feeling of optimism and well-being, along with pain relief, and it is used for daytime smoking. *Cannabis indica* provides an effect described as a "body high" that promotes relaxation, stress relief, and an overall sense of calm. *Cannabis indicas* are supposedly effective for insomnia and are therefore used in the late evening (Hazekamp & Fishedick, 2012). In higher doses of *C. sativa* or *C. indica,* people can also experience hallucinations, delusions, and psychosis (NIDA, 2017c).

Substance misuse

Some marijuana users extend their partnership with marijuana well beyond nutritional, recreational, and medicinal use. Marijuana can be a substance of misuse, becoming habitual and detrimental to life, leaving the user unable to stop using even when it is identified as causing problems. Research suggests that between 9% and 30% of marijuana users may develop some degree of marijuana use disorder (NIDA, 2017c). People who begin using marijuana before the age of 18 are 4 to 7 times more likely than those who start using marijuana as adults to develop a marijuana use disorder (NIDA, 2017c). There are no reports in the United States of anyone dying from marijuana use alone (NIDA, 2017c); however, people do report disturbing effects, such as anxiety and paranoia. There is an increase in the reports of such adverse effects to emergency departments, thought to be related to the rise in marijuana food manufacture and the cultivation of plants with higher THC levels (NIDA, 2017c).

According to the UNODC, as of 2015 there were some 183 million users of marijuana, roughly 3.8% of the global population, making marijuana the most widely used illicit drug in the world (UNODC, 2017a, 2017b). In the Western Hemisphere, marijuana use is on the rise. Estimates for the Americas show an increase from 37.6 million people (or 6.5% of the population aged 15 to 64 years) who used marijuana in 2005 to 49.2 million (or 7.5% of the population aged 15 to 64 years) in 2015 (UNODC, 2017a, 2017b).

Persons who stop using marijuana after a long period of use can have withdrawal symptoms like those of nicotine withdrawal: irritability, sleep problems, anxiety, decreased appetite, and craving – which can be the impetus for relapse. Withdrawal symptoms, however, are generally mild and peak a few days after use has stopped. They gradually disappear within about 2 weeks (NIDA, 2017c). Currently no medications have been approved by the FDA for treating marijuana use disorder or addiction, although promising research is under way to find medications to treat withdrawal symptoms such as sleep disturbances and to ease cravings and other effects of marijuana (NIDA, 2017a, 2017c). Behavioral therapies (see Chapter 4) that are available are similar to those employed for treating other substance misuse disorders and addictions. Treatments that have shown evidence of effectiveness include motivational enhancement to help people develop their own incentive to stay in treatment; cognitive-behavioral therapies to teach strategies for avoiding drug use and its triggers and for effectively managing stress; and incentives such as vouchers or small cash rewards for staying drug free (NIDA, 2017c).

Case study 1-1: What is this plant?

James is part of an interdisciplinary panel offering a community workshop promoting health literacy related to marijuana use by high school seniors preparing to go to college. The panel starts the day by listening to "burning questions" that participants want to be sure will get answered during the workshop. Mrs. Jones, a workshop participant, asks, "Why does the FDA allow all those marijuana products in health food stores? My son is a football player and very health conscious, but I think he's getting himself addicted by eating that hemp food. What should I do?" When asked about her concern, she then states that her son's grades have gone from A's to C's this semester. He stays in his bedroom much of the time after school and when he comes

out of his room for dinner he smells strange and his eyes are red. Mrs. Jones says that she does not think that he is smoking marijuana because he gets up every morning early for school and does not appear to be hung over.

Questions

1. What botanical information might you share with Mrs. Jones?
2. What is the FDA status of hemp?
3. Is there any other information you think you might share with Mrs. Jones, given her son's behavior changes?

Answers

1. Hemp products are indeed made from the same plant (*Cannabis sativa*) as marijuana, but hemp food products do not typically cause someone to "get high." These products are high in protein and nutrients, and such products have been used as food for centuries. Tell Mrs. Jones that her son's athleticism may be what drew him to a high-protein diet.
2. Hemp is regulated as a "food" (generally recognized as safe, or GRAS) by the FDA and is safe for consumption. Therefore, Mrs. Jones's son can legally purchase hemp food products in the health food store.
3. Ask Mrs. Jones if she has considered that her son might be showing signs of possible drug use. Tell her that people who smoke marijuana are not typically hung over in the morning. Comment that her son's interest in hemp food products may be an extension of an interest in marijuana use. Suggest that she ask her son if he is smoking marijuana or taking any other drugs.

Conclusion

Marijuana is a plant that is the most commonly used illicit drug in the world. Different species of marijuana have different effects. *Cannabis sativa,* the most common species, is known to have hallucinogenic as well as energizing effects and seems to promote optimism, whereas *Cannabis indica,* the species whose resin is used in hashish, produces whole-body relaxation and calming. Hemp derives from a strain of *Cannabis sativa* plant with a low THC level, and it has proved useful for the manufacture of such fiber-based products as rope and as the basis of nutritious food products.

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CHAPTER 2: THE ENDOCANNABINOID SYSTEM AND DRUG DEVELOPMENT

The study of any drug development from a single plant such as marijuana, with its extensive cultural history, takes time, resources, and innovation. Because the marijuana drug market still includes massive amounts of whole-plant material, the trajectory for any drug development would involve people and professionals from many different societal and scientific paths. Agricultural scientists working where marijuana may be grown legally can develop plant cultivars, but traditional vendors looking for plants with higher delta-9-tetrahydrocannabinol (THC) levels are no doubt working in the field as well. High-THC-level marijuana is what is being sold on the recreational market. Currently, more than 700 cultivars have been identified for *Cannabis sativa* and *C. indica* (Hazekamp & Fishedick, 2012).

Another group exists with expertise in pharmacognosy, pharmaceutical and natural product development. They study plants and their constituents to discover mechanisms of action for observed effects in humans that might be replicated in synthetic drug development. One of the primary foci of this work with marijuana has been to discover how to get the known benefits from the plant without its psychoactive effects. Plant science has determined that there are two major neuroactive phytocannabinoids (plant constituents) responsible for some of the actions in the *Cannabis* plant, THC and cannabidiol (CBD; National Institute on Drug Abuse [NIDA], 2017c). Much of the pharmaceutical drug development has been focused on separating and studying these two constituents from marijuana. The psychoactive effect attributed to THC is the primary concern of people involved in crude plant development for recreational use. Marijuana contains more than 500 identified phytochemical constituents, of which at least 104 are cannabinoids (Fasinu, Phillips, ElSohly, & Walker, 2016). Marijuana's "phytocannabinoid" compounds have potential central nervous system action, with heterogeneous psychoactive effects and neuropharmacological actions. The term phytocannabinoid refers to constituents that occur naturally in the marijuana plant, as opposed to endocannabinoids, which occur naturally in lipid-derived neurotransmitters found in the human body. Research on the endocannabinoid system (ECS) is an emerging field attempting to answer public demand for greater scientific understanding of the marijuana plant at the center of the ongoing sociopolitical controversy over self-medication with marijuana. Healthcare professionals, parental advocates, and end users pose the questions that drive the demand for drug development. The purpose of this chapter is to highlight the state of the science, including crude plant-drug development and understanding of the ECS, a study in which innovation spawned from marijuana and other plant-drug development is gaining significant scientific momentum (Kendall & Alexander, 2017).

THC is responsible for the euphoric and psychotomimetic effects of marijuana, whereas CBD does not have these results but may have anxiolytic and other medicinal effects (Ligresti, De Petrocellis, & Di Marzo, 2016). The data most often utilized for forensic, legislative, and medicinal purposes are examination for the presence of THC and tests that distinguish hemp (fiber) from marijuana (medicinal). However, the most widely studied and preferred medicinal constituent is CBD. For example, the U.S. Food and Drug Administration (FDA) has approved two cannabinoid medications for cancer-related, chemotherapy-induced nausea and vomiting: dronabinol (brand name Marinol) and the synthetic cannabinoid nabilone (discussed below). Cannabinoids are known to interact with the cytochrome P450 enzyme system in the liver involved in drug metabolism. This situation raises concern about drug-drug (cannabinoid) and drug-herb (marijuana) interactions. One study, cited on the website of the National Cancer Institute (NCI, 2017), researched the drug-herb effects of marijuana in herbal tea form in people with cancer who were being treated with the intravenous chemotherapeutic agents irinotecan and docetaxel. Although marijuana tea did not significantly influence exposure to and clearance of the chemotherapeutic agents in the study, the effects of inhalation or oral ingestion of cannabinoids have yet to be studied. CBD has been shown to have anticonvulsant properties and may be helpful in the treatment of epilepsy (see Chapter 3).

Determination of the best plant sources of medicinal-grade marijuana typically involves analysis of 28 compounds, using a system such as principle component analysis. Marijuana extracts have variable amounts of THC depending upon the plant variety used in the preparation. Higher THC-to-CBD ratios are associated with more prominent psychoactivity (euphoric, relaxant, and anxiogenic effects), whereas low ratios of THC-to-CBD are more sedating (Fasinu et al., 2016). *Cannabis indica* has a higher CBD-to-THC ratio.

THC exerts its pharmacologic effects by mimicking the body's own cannabinoid neurotransmitters by binding to two G-protein-coupled cell membrane receptors, referred to as the cannabinoid type 1 (CB1) and type 2 (CB2) receptors. CBD, on the other hand, does not bind to CB1 or CB2 receptors, which is thought to explain why it lacks psychoactive activity. However, CBD does have a number of pharmacological effects. It acts on receptors involved in the sensation of pain and cold, as well as affects pain response and sensitivity to heat (Bisogno et al., 2001).

CBD is administered orally or by smoking and vaporization. The CBD oil that comes in a capsule is poorly absorbed from the gastrointestinal tract, with bioavailability estimated at 6%. Vaporization requires special equipment and is therefore less accessible than the traditional way of smoking whole leaf marijuana. CBD is rapidly absorbed into the tissues, with a high volume of distribution. According to Fasinu and colleagues (2016), CBD's estimated half-life is from 18 to 32 hours, with a clearance of 57.6 to 93.6 liters per hour.

CBD is known to have anticonvulsant properties, and supporting evidence exists for its use in the treatment of epilepsy (see Chapter 3). CBD also displays powerful activity against methicillin-resistant *Staphylococcus aureus* (MRSA), with a minimum inhibitory concentration (MIC) of 0.5 to 2 mg/mL. The MIC is the lowest concentration of CBD that would prevent visible growth of MRSA. A lower MIC antimicrobial has a greater ability to eradicate microbes. All five major cannabinoids (CBD, cannabichromene, cannabigerol, THC, and cannabinol) show potent activity against a variety of MRSA strains in vitro (Appendino et al., 2008). Research continues in the search for cannabinoids that may prove useful as antibiotics, antiseptics, and agents against malaria and leishmaniasis (Russo, 2011).

When marijuana is inhaled, either as combusted or vaporized plant matter, THC reaches peak concentration in 2 to 5 minutes, followed by a rapid drop-off. Inhaled cannabinoids reach their peak concentration in 5 to 10 minutes, declining rapidly for a period of 30 minutes (Fasinu et al., 2016). The action of THC in inhaled oils, as one might find in electronic cigarettes, is not yet known (Abrams, 2016). Orally ingested marijuana has a lower and variable bioavailability. It may take hours for THC to reach peak plasma concentrations, which then remain elevated with a terminal half-life of 25 to 30 hours (Abrams, 2016). When THC is ingested, it is initially metabolized in the liver to a psychoactive substance called 11-hydroxy-THC, explaining why people eating marijuana-baked products or capsules may report a more significant psychoactive effect compared with those who inhale it (Abrams, 2016).

Dosing differences

Clinical studies have employed a wide range of preparations. For whole plant (leaf and seed), dosage is titrated for effect, much as is customary in the practice of traditional herbalism. Documented standard dosages exist, in the traditional Chinese *Materia Medica,* for example, but in marijuana use, titration and customization based on individual need are the norm, and they are required when using the plant as a self-care simple (single-herb remedy) or in formulations. When dealing with THC, making standard dosage recommendations may still be difficult because people's tolerance for the psychoactive effects of THC can vary greatly. As will be shown in this course, people who engage in marijuana use learn to titrate their doses based on the type of plant product they have purchased, the form in which they plan to use the plant, the length of time they have been taking marijuana, and their understanding of the effects of the plant. Titration of marijuana dose that leads to a sliding scale of sorts is often derived through trial and error. Uncomfortable psychoactive experiences related to the marijuana "high" are a barometer for what constitutes an error. This approach based on adaptation response can be compared to the person with diabetes who is taking insulin for the first time and may have some uncomfortable episodes of hypoglycemia resulting from taking too much insulin or exercising too much and not eating enough food to cover the exercise and insulin dose.

Dosing with a marijuana constituent such as THC or CBD, or for that matter with an FDA-approved drug such as dronabinol or nabilone (discussed later in the chapter), really challenges the user and healthcare professionals who care for them to be mindful of the person's unique response to the herb or drug. There may be research studies, publications, and clinical guidelines that provide standardized dosing information. However, the psychoactive nature of THC still requires that it be considered for titration based on a user's response. The ambiguity inherent in plant medicine practice generally is evidenced when partnering with marijuana. That ambiguity resolves over time as users and healthcare professionals become more knowledgeable concerning the qualities and actions of the plant as medicine upon various individuals.

PHARMACEUTICAL DRUG DEVELOPMENT

A major area of interest of drug development from the marijuana plant is the treatment of nausea and vomiting in people undergoing chemotherapy for cancer. Through the years, many people with cancer have grown or acquired whole-plant marijuana for use in relieving these symptoms. Dronabinol and nabilone are two pharmaceutical-grade drugs that are approved by the FDA for the prevention and treatment of nausea and vomiting in people with cancer. Meta-analyses of controlled trials have found these drugs to be helpful when compared with placebo (NCI, 2017). Although THC has been the focus of drug development since 1964, other phytocannabinoids of therapeutic interest, including tetrahydrocannabivarin, cannabigerol, and cannabichromene, have also been explored (Russo, 2011). There is also significant market demand for research on whole-plant marijuana. Sativex (nabiximols), a standardized oromucosal whole-cannabis extract is approved for prescription in 29 countries (but not in the United States; Russo & Marcu, as cited in Kendall & Alexander, 2017). Although many of the drugs on the market are originally derived from plants, many more are ultimately manufactured as synthetic copies of original plant materials or their constituents. Standardization of constituents in medicinal plants – including marijuana – that are so easily subject to environmental changes is challenging for manufacturers and researchers alike.

Constituents in marijuana that are being studied in human health include terpenoids (Russo, 2011), which share a precursor with phytocannabinoids. Terpenoids are plant components that contribute to flavor and taste in foods. They are quite potent and affect animal and even human behavior when inhaled from the air in small amounts. They display unique therapeutic effects that may contribute meaningfully to the "entourage effects" (synergy) of marijuana-based medicinal extracts (Russo, 2011). An emphasis of research is on phytocannabinoid-terpenoid *interactions,* positive synergistic interactions that may in combination offer much in the treatment of pain, inflammation, depression, anxiety, addiction, epilepsy, cancer, and fungal and bacterial infections (including MRSA). Methods for investigating entourage effects in future experiments are being developed. Phytocannabinoid-terpenoid synergy, if supported by experimentation, could potentially lead to the development of new therapeutic products and drugs from marijuana. Noncannabinoid plant components in marijuana may actually work as antidotes to the intoxicating effects of THC, making THC more therapeutically useful (Russo, 2011).

Dronabinol and nabilone

Dronabinol and nabilone are currently the only cannabinoid drugs that have moved through the drug development process and achieved FDA approval status. Dronabinol (brand names Marinol and Syndros) is pure THC in an oil-filled, soft gelatin capsule. Nabilone is a synthetic analogue of THC. Designs for synthetic drugs are often derived from the chemical structures of original plants or constituents. Nabilone comes as a capsule and as a solution (liquid) to take by mouth. Dronabinol capsules and solution used to treat nausea and vomiting caused by chemotherapy are usually taken 1 to 3 hours before chemotherapy and then every 2 to 4 hours after chemotherapy, for a total of four to six doses a day. The first dose of the solution is usually taken on an empty stomach at least 30 minutes before eating, but the following doses can be taken with or without food. When dronabinol capsules and solution are used to increase appetite, they are usually taken twice a day, about an hour before lunch and supper. The person swallows the dronabinol solution with a full glass of water (6 to 8 ounces). Dronabinol may be habit forming. People who are taking disulfiram (Antabuse) or metronidazole (trade name Flagyl; also a component of Pylera) or who have taken these medications within 2 weeks will most likely be advised not to take dronabinol. People should not drink alcoholic beverages while they are taking dronabinol because alcohol can make the side effects from dronabinol worse. Also, dronabinol may cause dizziness, lightheadedness, and orthostatic hypotension. People on dronabinol should not eat grapefruit or drink grapefruit juice because of possible drug-plant interaction (Prescribers Digital Reference [PDR], 2018). Dronabinol oil capsules are also contraindicated in those with sesame-oil sensitivities (PDR, 2018).

MECHANISMS OF ACTION

Cannabinoids are a group of 21-carbon-containing terpenophenolic compounds produced only by marijuana species. Although THC is the primary psychoactive ingredient in phytocannabinoids, other known compounds with biologic activity are cannabinol, CBD, cannabichromene, cannabigerol, tetrahydrocannabivarin, and delta-8-THC. CBD is thought to have significant analgesic, anti-inflammatory, and anxiolytic activity without the psychoactive effect of THC (Fasinu et al., 2016). As mentioned previously, THC mimics endogenous cannabinoid neurotransmitters by binding to CB1 and CB2 receptors. CB1 receptors are found primarily in the brain and peripheral tissues, whereas CB2 receptors are concentrated in immune and hematopoietic cells. According to Fasinu and colleagues (2016, p. 783), "CB1 receptors are located at presynaptic junctions where they are involved in the regulation of ion channels and modulation of the release of dopaminergic, γ-aminobutyric acid (GABA), glutamatergic, serotoninergic, adrenergic, and cholinergic neurotransmitters."

The endocannabinoid system

The ECS is defined as the endogenous signaling system that comprises cannabinoid receptors; endogenous cannabinoid receptor ligands (small molecule lipids), also known as endocannabinoids; and enzymes responsible for the production and degradation of endocannabinoids (Kendall & Alexander, 2017). Endocannabinoids in the brain, such as anandamide or 2-AG, are neurotransmitters that indirectly affect dopamine signals by modifying the activity of other neurotransmitters such as GABA that help the brain develop, learn, adapt, and navigate a complex world. Endocannabinoid molecules closely resemble THC. Because THC is so similar to the brain's own endocannabinoids, smoking marijuana directly affects the brain of the user. In the user's brain, THC competes with the brain's endocannabinoids to bind with cannabinoid receptors on neurons that regulate dopamine activity. Among other effects, THC reduces the release of GABA in the corpus striatum part of the brain. This reduction causes nearby dopamine neurons to release more dopamine. The increased dopamine release produces the positive feelings of the marijuana high. THC can activate cannabinoid receptors throughout the brain, altering healthy communication within the brain and between the brain and the rest of the body. This process can negatively affect emotions, movement, learning, decision making, and memory (NIDA, 2017d).

The ECS is affected by stress, food intake, and behavioral change. Endocannabinoids act like dopamine in that they bind to specific receptor proteins located on the surface of some cells. A presynaptic dopamine neuron can produce endocannabinoid molecules that bind to cannabinoid receptors on adjacent GABA neurons, thereby reducing the amount of GABA being released (Fasinu et al., 2016). Inhibiting GABA neurons boosts the dopamine signal. The ECS functionally impacts synaptic communication with direct modulatory effects on pain perception, eating, anxiety, learning, memory, and growth and development in the central nervous system, as well as motor control, immune-competency, tumor cell proliferation,

and inflammation. The endocannabinoids may also "exert effects via non-CB receptors as well, such as through certain serotonin or vanilloid receptor subtypes" (Fasinu et al., 2016, p. 784). Cannabinoids and their receptors are involved in basic physiology and pathophysiology, including roles in gene expression and possibly in mediating complex disease processes such as schizophrenia, cancer, neurodegeneration, and chronic pain. In addition to the brain, the ECS is found in many parts of the body. For example, the activation of cannabinoid receptors by endocannabinoids on epidermal cells regulates normal function of the skin as a barrier. Engaged CB1 and CB2 receptors can modify the proliferation, differentiation, and apoptosis of epidermal cells. Endocannabinoids also suppress inflammation in the epidermis.

Russo and others are exploring the hypothesis of "endocannabinoid deficiency" and its relationship to people's positive responses to diseases when dosed with marijuana's phytocannabinoids. First posited in 2001, this hypothesis was based on genetic overlap and comorbidity, patterns of symptomatology that could be mediated by the ECS, and the finding that exogenous cannabinoid treatment frequently provided symptomatic benefit. However, objective support and formal clinical trial data have been lacking. Currently, however, "statistically significant differences in cerebrospinal fluid anandamide levels have been documented in migraineurs," and imaging studies have demonstrated ECS deficiency in posttraumatic stress disorder (Russo, 2016, p. 155). Additional studies have provided a firmer foundation for the notion of ECS deficiency, and clinical data have also produced evidence for decreased pain, improved sleep, and other benefits to cannabinoid treatment and adjunctive lifestyle approaches affecting the ECS (Russo, 2016).

ADVERSE EFFECTS, SAFETY, AND POTENTIAL

Drug-herb interactions

One reason for the record of safe use of herbal remedies is that plants are made up of hundreds of different biochemical constituents. Used in whole form, whether decocted as tea or used as an extract or salve, the action of whole-plant therapies is complex when looked at through a reductionist lens. The chemical constituents in plants occur in very small amounts. Herbs, although they have healing properties and the ability to create change and can even cause chemical reactions in the body, are not pharmaceutical drugs typically produced from one substance. They are much more complex. When people ingest, apply, or inhale herbs, they are taking in very small "doses" of particular substances that are in a natural, rather than synthetic, state and are in formulation, so to speak, as they occur in nature. The safe use of whole plants is related to the use of a plant in its complex natural state. Often the botanical science reveals that medicinal plants contain constituents in balance, with seemingly opposing actions. Plant pharmacy is replete with examples of such balance or contradiction. For example, the hypericin constituent in St. John's wort (*Hypericum perforatum*) "induces the cytochrome P450 system (inducing CYP3A4 in hepatocyte cells) and at the same time contains the bioflavonoid quercetin, which is a 3A4 inhibitor" (Libster, 2002, p. 74). However, when people decide to use a standardized extract of a single constituent of an herb, such as hypericin, much like a drug, or use an herb in a form that departs from traditional use, the historical safety record is no longer applicable. For example, if the safety record of traditional medicinal use of garlic is related to eating the fresh chopped bulb in food or as an infused oil, new safety data will have to be collected for use of powdered garlic tablets. Whereas safety "information" related to traditional use of herbs is shared through oral tradition (e.g., where and when to harvest, how to gather and prepare and apply, how much to take and when) biomedical use of herbs compels research and further gathering of population safety information about new forms of herbal remedies and applications. When herbs are used in the treatment of biomedically defined diseases, the same safety standards are followed as are used with drugs. Marijuana has been used for centuries and is relatively safe (see Chapters 3 through 5) when compared with other illicit drugs. However, when herbs' constituents are removed and placed in pharmaceutical single-constituent drug form, a new history of use begins. Safety cannot be inferred for these or any whole-plant products that diverge from traditional use. Marijuana-based pharmaceutical drugs and innovative products such as cannabinoid-terpenoid synergy drugs require a clinical-trial evidence base.

Another risk associated with any plant medicine use is adulteration. The American Botanical Council hosts the Botanical Adulterants Program, in which various industry partners "adopt" an herb that is then watched for quality and purity in the marketplace, along with accidental and intentional adulteration. It has been claimed that marijuana cultivars are greatly increasing in THC potency (McLaren, Swift, Dillon & Allsop, 2008) and that scientific testing of marijuana is needed to monitor potency, contamination, and adulteration to address any potential or actual public health risks. There are also concerns about engineered marijuana-based products. One example is "Spice," also called "K2," "herbal incense," or "fake weed." This product consists of shredded, dried plant material sprayed with chemicals designed to act on the same brain cell receptors as THC. The chemicals are often much more powerful and unpredictable. Some of these products are labeled "not for human consumption," and many are now illegal (NIDA, 2016). But new chemical compounds are constantly being manufactured. The effects, like the ingredients, often vary, and users may present to an emergency room with rapid heart rate, vomiting, and negative mental responses, including hallucinations, after using these substances (NIDA, 2016).

CBD has shown potent inhibitory activity against cytochrome P2C, CYP2D6, and CYP3A isoforms in preclinical studies, raising concerns of drug-drug interactions with other substrates of the enzymes (Jiang, Yamaori, Okamoto, Yamamoto, & Watanabe, 2013). In one study of the interaction of CBD and clobazam, an epilepsy medication, patients began taking CBD and clobazam concurrently. After 4 weeks, CBD caused a greater than 60% increase in mean plasma levels of clobazam and a 500% increase in mean plasma levels of clobazam's major metabolite, N-desmethylclobazam (Geffrey, Pollack, Bruno, & Thiele, 2015). Because most commercially available antiepileptic drugs are metabolized through the CYP pathways, drug interactions with CBD may occur. CYP3A4 inducers such as phenytoin and carbamazepine may also induce the metabolism of CBD. At therapeutic dosages, however, CBD is generally well tolerated and has an acceptable safety profile (Geffrey et al., 2015).

Dronabinol and nabilone can be habit forming, and as stated above, it is recommended that people not drink alcohol while taking these drugs. Severe adverse effects of nabilone include increased heart rate, hallucinations, and difficulty thinking. Severe adverse effects of dronabinol are seizures, increased heart rate, and fainting (PDR, 2018).

According to a 1999 report by the Institute of Medicine (IOM; now the Health and Medicine Division of the National Academies), marijuana's adverse effects are "within the range of effects tolerated for other medications." This is not to say that marijuana is completely without adverse effects, especially when consumed in uncontrolled circumstances (see Chapter 5). There are chronic effects related to THC and chronic smoking. Marijuana smoking, as with all smoking, may be associated with increased risk of cancer and lung damage (IOM, 1999). The primary adverse effect of acute marijuana use is identified as diminished psychomotor ability. People should be advised not to operate heavy equipment or vehicles when under the influence

of marijuana, THC, or any cannabinoid drug. Some people also experience dysphoria (a feeling of unease, discomfort, and generalized dissatisfaction). According to the IOM report (1999), older people with no previous experience with taking marijuana often experience psychological effects that are disturbing to them, such as disorientation after being treated with THC. These effects appear to be felt more with oral THC than smoked marijuana. In 2001, researchers who interviewed 3,882 survivors of myocardial infarction (MI) found that the risk for developing MI was 4.8 times higher than average within the hour immediately after marijuana use (Mittleman, Lewis, Maclure, Sherwood, & Muller, 2001). After MI, mortality is significantly higher in marijuana users than in the general population (Thomas, Kloner, & Rezkalla, 2014). On the other hand, a recent study of 5,113 adult participants' coronary artery risk found no association with the incidence of cardiovascular disease from cumulative lifetime or recent use of marijuana (Reis et al., 2017).

A study of women who smoked marijuana at least once a month during pregnancy found impaired placental development, as indicated through analysis of human tissue obtained at about 7 weeks of gestation. It also found that CB1 and CB2 were decreased in the placenta of marijuana smokers as compared to pregnant nonsmokers (Chang et al., 2017). Marijuana use during pregnancy has been associated with low birth weight and increased risk of both brain and behavioral problems in babies (NIDA, 2017a). Some THC can get into breast milk if a mother is using marijuana regularly (NIDA, 2017a).

Addiction and overdose

Marijuana can lead to a substance use disorder and addiction. Between 9% and 30% of marijuana users may develop some degree of disorder, and individuals who begin using marijuana before the age of 18 are 4 to 7 times more likely than adults to develop a marijuana use disorder (NIDA, 2017e). People who already have an alcohol use disorder and smoke marijuana may be at greater risk of their alcohol use disorder worsening (NIDA, 2017d).

Overdose from marijuana smoking or eating is not likely, according to the NIDA (2017d), although people, particularly children, do report suffering adverse effects from ingesting too many edible marijuana products (see Chapter 5). People who overdose on marijuana can experience extreme anxiety, panic, psychotic reactions, and paranoia. Perceptions, judgment, and coordination can also be affected by marijuana. The IOM report (1999) identifies a "distinctive" but mild and short-lived withdrawal syndrome that includes restlessness, irritability, agitation, insomnia, sleep disturbance, nausea, and cramping. (See Table 2-1.)

Table 2-1: Symptoms of Overuse of and Withdrawal from Marijuana

Common Symptoms of Overuse of Marijuana	Common Symptoms of Withdrawal From Marijuana
• Anxiety. • Fear. • Panic. • Suspicion and paranoia. • Hallucinations (visual, auditory).	• Irritability. • Insomnia and strange dreams. • Anorexia. • Restlessness and headache. • Aggression.

Note. From Western Schools, © 2018.

Some are considering the re-examination of certain simple interventions documented in historical and traditional sources for the treatment of the uncomfortable sensations sometimes attributed to larger doses of marijuana. A 19th century text, *King's Dispensatory,* suggests, for example, that the effects of *Cannabis indica* can be mitigated by lemon juice, coffee, emetics, and cold applications (Felter & Lloyd, 1898/1983). Opportunity exists for adjunctive and translational research in this area of caring for those in marijuana treatment who may be experiencing adverse effects of the herb or drug.

Is marijuana a gateway drug?

Understanding the gateway process involves sequence (use of a gateway drug leading to use of hard drugs), association (increased likelihood of hard drug use in those who use marijuana), and, controversially, causation. Researchers have demonstrated that marijuana use occurs prior to use of harder drugs such as cocaine and heroin and that, relative to nonusers, marijuana users are considerably more likely to subsequently report use of hard drugs. However, the evidence for causation, or that marijuana use exerts a causal influence on the likelihood of using other illicit drugs, has been less clear (Agrawal & Lynsky, 2013).

Animal studies have shown that exposure to addictive substances like THC can change how the brain responds to other drugs, particularly as regards response-reward mechanisms that can signal addiction behaviors. This finding suggests that marijuana may potentially be a gateway drug for some users; however, it is important to note that factors other than these biological mechanisms, such as a person's social environment, are also critical in determining a person's further risk for drug use. Trends in people's use of marijuana leading to further drug use can also be explained by marijuana often being one of the more accessible substances, along with alcohol and tobacco (NIDA, 2017b).

According to Miech, Patrick, O'Malley, and Johnston (2017), since 2013, attending college has become a substantially stronger risk factor for marijuana use. Before 2013, adolescents in college who had never used marijuana by the 12th grade were 17% to 22% more likely to use marijuana in the past 12 months than were their age peers who were not in college. This higher relative risk steadily increased and more than doubled in the following years to 31% in 2013, 41% in 2014, and 51% in 2015 (Miech, et al., 2017). Academic leaders are beginning to consider interventions for marijuana use as they have for binge drinking and other lifestyle choices and behaviors that can affect education, socialization, and health.

There are some in the criminal justice field, for example, who now argue that the gateway drug theory is an "unjustified oversimplification of the dynamics of drug use reflecting the interests of certain stakeholder rather than wise social policy" (Kleinig, 2015, p. 971). The drugs are a branch pattern of the issues of the tree and its roots. A lack of or poor parenting, living in the wrong neighborhood, the need to belong, lack of self-esteem, or whatever it is that makes a self-destructive dependence attractive is the actual "gateway." Marijuana dependence is discussed further in Chapter 4.

Conclusion

Marijuana (whole plant) is widely used by Americans in self-care despite its illegal status. Drug development includes not only THC and CBD products, but also production of whole-plant extracts. The IOM report of 1999 on the state of the science regarding marijuana concluded that cannabinoids have a natural role in pain modulation, control of movement, immune response, and memory. The report concluded that the brain can develop tolerance to cannabinoids but the potential for dependence on marijuana is "observed under a narrower range of conditions than with benzodiazepines, opiates, cocaine, or nicotine" (IOM, 1999, p. 2). The recommendations of the IOM concluded that different cannabinoids appear to have different effects, and that cannabinoid research should include, but not be restricted to, effects attributable to THC alone. Clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of developing rapid-onset, reliable, and safe delivery systems. Research on the ECS presents new opportunities for translational research, medical science, nursing and behavioral healthcare approaches, and drug development.

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CHAPTER 3: CLINICAL RESEARCH AND THERAPEUTIC USES OF MARIJUANA

This chapter focuses on some of the findings from research on the use of marijuana in the treatment of disease and other health challenges. Marijuana use poses its own concerns related to substance use. The literature suggests that healthcare professionals are often unclear as to how to best approach the treatment of a dual diagnosis of substance use disorder – such as cannabis use disorder – and a medical or psychiatric diagnosis (Minkoff, 2001). Integrated care for persons with dual diagnoses is complex. Therefore, this chapter will deal with the evidence for positive medicinal effects of marijuana use. (Treatment strategies for marijuana use, dependence, and abuse are discussed further in Chapter 4.) This chapter also focuses on specific examples of research and use of marijuana in the treatment of persons with epilepsy, mental illness, and cancer.

OVERVIEW OF CLINICAL RESEARCH

Supporting marijuana use with clinical re-search or population studies is a challenge, given its current legal status in the United States. When intervention studies are sanctioned, there is a second level of challenge because the most common use of marijuana is as a smoked whole leaf or resin. To conduct a proper clinical trial of any herb, in this case marijuana, the preferred intervention would be to use a standardized form, meaning that each product used in the study would be the same. Standardization in botanical and pharmaceutical research seeks to decrease the number of variables influencing outcomes in studies and then in clinical practice. The possibility for standardization of marijuana as crude plant material begins with agriculture and then subsequent evaluations of plant constituents thought to be responsible for the effects. In the case of marijuana, growers and manufacturers seek to standardize or ensure the amount of delta-9-tetrahydrocannabinol (THC). However, hundreds of other constituents are influenced during the growing cycle by the environment, growing techniques, harvesting, and storage. Some of the best product for use in clinical trials may be that which comes from the marijuana growers in states where the plant is legal and grown according to state law.

Another challenge for an experimental study on marijuana is the need for producing a detailed plan for teaching and monitoring the techniques that each participant would follow in preparing and using the marijuana he or she was given during the trial. Consistency, accuracy, and veracity are difficult to ensure in any trial. Alternatively, a study design could utilize a central location for participants to use as they smoke what they were given by investigators. Researchers who engage in natural medicine development must consider such details. According to a researcher at the Tufts Center for the Study of Drug Development, the research that meets the "gold standard" in American science for bringing one single new drug to the market was estimated to cost $1.3 billion (U.S. Food and Drug Administration [FDA], 2018; Feyman, 2014). It is unclear when and if the financial burdens can be offset by any gains that the pharmaceutical industry would ultimately receive. The notion that medicinal plant research (on any plant) is *best* informed by clinical trials consistently poses challenges to the industry. A plant cannot be patented and protected so that a company can recoup losses incurred during scientific development. Therefore, waiting for clinical trials on whole-leaf marijuana or seed is not likely to be a productive public health strategy given the current amount of national activity with the plant.

Research groups across the country, such as the Imaging Data in Emerging Adults with Addiction Consortium, a multisite group including a McLean Hospital Harvard University Neuroscience

professor, and the University of California Los Angeles Cannabinoid Affinity Group (http://www.bri.ucla.edu/research/affinity-groups/cannabinoid), are responding to the urgent need for research on this matter. However, much of the published data available for decision making come from meta-analyses and literature reviews of retrospective and population studies. Quite a few of these studies have been conducted in Europe. If a population of 10 or 1,000 people are asked about their marijuana use, the data collected, although helpful, cannot be employed in determining causation or prediction of outcome in a population or the one person seeking care. As many marijuana products and techniques could exist as there are people being surveyed. Hence, these studies can only provide general information of emerging patterns of use. Without population studies of people who smoke the same cultivar of marijuana in the same way, marijuana growers and users could argue against the merit of population studies. An equivalent example would be assigning toxicity status to all peanuts in the United States because a retrospective population study showed that many people experienced reactions to peanuts. Peanut farmers would demand that researchers declare which peanut crops and what product form (e.g., whole in shell, roasted, peanut butter) they had found to be the problem agents. Clinical trials that seek to identify causation are hard pressed to do so without attention to detail, both of plant constituents and users' idiosyncrasies.

Clinical trials on marijuana are presented here for review when available; however, much of the current published data come, as mentioned previously, from retrospective population studies. In addition to the limitations already discussed, these population studies typically rely on self-report, a method of data collection lacking rigor, especially in studies done in places where marijuana use is against the law. Additional data from population studies that address concerns about risk related to marijuana use are presented in Chapter 5 of this course.

COMMON MEDICINAL USES AND EVIDENCE OF EFFECTIVENESS FOR MARIJUANA AND HEMP

Epilepsy

Approximately 3.4 million people in the United States have epilepsy (Epilepsy Foundation, 2014), and nearly 30% of those people are unresponsive to standard medications (Detyniecki & Hirsch, 2015). Symptomatic treatment of epilepsy is the most common strategy; however, antiepileptic drugs often have troubling side effects and fail in the treatment of temporal lobe epilepsy (Soltesz et al., 2015). It is understandable that parents of children who must wear crash helmets because of seizures uncontrolled by current pharmaceutical treatments would consider reaching for marijuana or a marijuana-based drug for their children. It may seem a rational choice when weighing the extensive body of historical (Felter & Lloyd, 1898/1983) and anecdotal clinical evidence for successful treatment with marijuana against the risk that a child faces every time he or she suffers a seizure. To date, there is a lack of quality clinical research evidence with sufficient sample sizes to support or negate marijuana's traditional use in the treatment of seizures in people of any age. However, evidence is increasing that physiological states such as stress and pathophysiological conditions such as epilepsy modify the endocannabinoid signaling system (ECS; see Chapter 2).

In epilepsy, cannabinoid type 1 (CB1) receptors are markedly downregulated throughout the hippocampus in the acute phase shortly after the initiating insult, but they are upregulated in the chronic phase of the disorder (Soltesz et al., 2015). "The concurrent upregulation of CB1 receptors on GABAergic terminals and downregulation of CB1 receptors on glutamatergic axons that takes place in epilepsy may mechanistically contribute to seizures" (Soltesz et al., 2015, p. 272), but the importance of these biological processes is not well understood.

Studies have shown that the ECS plays an important role in modulating seizure activity, and deficiency or defect in the ECS is being studied as the possible cause for seizure. For example, one study published in the *New England Journal of Medicine* (Friedman & Devinsky, 2015) found lower levels of anandamide in cerebrospinal fluid in people with epilepsy than in healthy people serving as study controls. It is well documented that cannabinoids can provoke seizures, depending on the dosage, the content and ratio of the cannabidiol (CBD) and THC, and the underlying conditions in the patient. However, antiseizure medications that are already on the market are known also to provoke seizures in some patients and to be associated with clinically significant drug-drug interactions (Friedman & Devinsky, 2015). Current evidence also suggests that, although THC has anticonvulsive effects, at higher doses it can be proconvulsive (Detyniecki & Hirsch, 2015). However, phase III randomized controlled trials with oral CBD (Epidiolex) support efficacy and adequate safety profiles for children with Dravet syndrome (fever-induced epilepsy) and Lennox-Gastaut syndrome (childhood epilepsy) at doses of 10 and 20 mg/kg/day (O'Connell, Gloss, & Devinsky, 2017).

In 2014, the Cochrane Collaboration (Gloss & Vickrey, 2014) published its review on cannabinoid use in epilepsy. The stated goal of the review was to evaluate the literature for human studies that explored the effect of CBD on seizure freedom for 12 months or three times the longest usual seizure-free interval. The researchers rejected many of the studies they reviewed because they were not clinical trials. Four pioneering studies from 1980 to 1990 met all the inclusion criteria except the primary outcome. They were reviewed because they included adverse events, one of the secondary outcomes; however, the studies included inadequate numbers of participants for the drawing of conclusions. In one study, 15 patients with temporal lobe epilepsy, who experienced at least one generalized seizure weekly, received 200 mg to 300 mg of CBD daily or placebo for as long as 4.5 months. Investigators did observe that participants tolerated the CBD without toxicity. In the second study reviewed, 12 participants with uncontrolled seizures were treated with three capsules of sunflower oil (as placebo) or sunflower oil and 100 mg of CBD (300 mg daily) for the first week, followed by two capsules (200 mg daily) for 3 more weeks. There were no differences in seizure frequency between the two groups, although no details were given. The only side effect was mild drowsiness. In the third study, nine participants were randomized to groups receiving either 200 mg of CBD or placebo. Participants continued to take their regular medication plus CBD or placebo for 3 months. Two of four participants treated with CBD were seizure-free for the 3 months of treatment, and none of the five in the placebo group experienced improvement. No adverse effects were reported. In the fourth trial, 12 participants were treated with a single-blind placebo for 6 months, then a double-blind dose of 300 mg of CBD or placebo in a crossover trial lasting an additional 12 months. Ten patients in the trial did not experience changes in the frequency or character of seizures, but reported no adverse effects. The small sample size (48 total participants) and low quality of the study designs left the authors unable to draw conclusions from the review.

An Israeli multicenter trial was conducted with 74 children (aged 1 to 18 years) with refractory epilepsy (resistant to more than seven drugs) who were treated with marijuana oil for at least 3 months and an average of 6 months. Patients were treated with sublingual marijuana oil extract of one of two strains: "Cheese pie" and "Avidekel," both containing a CBD/THC ratio of 20:1, dissolved in olive oil, given three times daily. Daily dose ranged from 2 to 27 mg/kg/day. The response to treatment was evaluated as a parental-reported change in the mean monthly seizure frequency. Of the 74 patients, 66 (89%) reported reduction in seizure frequency. The reduction was 75% to 100%

in 13 patients (18%), 50% to 75% in 25 (34%), 25% to 50% in 9 (12%), and less than 25% in 19 (26%). Five (7%) patients reported aggravation of seizures, which led to discontinuation of use of the CBD (Tzadok et al., 2016).

Researchers suggest that future studies focus on the underlying mechanisms of alterations in the ECS in chronic epilepsy and other related pathological conditions, including autism, cell type-specific boosting of the ECS (for example, ECS-based gene therapy), physiological conditions that selectively control phasic or tonic ECS in vivo, and cannabinoid-based prophylaxis against epileptogenesis after various forms of brain injury (Soltesz et al., 2015).

Given the proven anticonvulsant effects from preclinical studies and the lack of psychoactive properties, CBD is considered to be a promising alternative if not a candidate as a medication for epilepsy. Its safety record is strong to date but the long-term effects of CBD are unknown. Researching the long-term neuropsychological effects in the developing brains of children is particularly important.

Glaucoma

Glaucoma treatment focuses on the continuous reduction of intraocular pressure (IOP). Because marijuana smoking and THC ingestion have been found to reduce IOP by 60% to 65%, oral and topical cannabinoids show promise for future use in glaucoma treatment. The concern with smoking is that the effects on IOP last only 3 to 4 hours and the amount of smoking necessary may be prohibitive (Green, 1998). In a 2001 study, eight participants were given either two drops (50 mL) of a 25-mg or 50-mg WIN55212-2 solution or placebo solution. WIN55212-2 is a synthetic and selective CB1 receptor agonist. These drops decreased intraocular pressure within 30 minutes of application in participants with resistant glaucoma (Porcella, Maxia, Gessa, & Pani, 2001). Studies continue to explore the relationship between the ECS and the pathophysiology of glaucoma as well as the long-term treatment of glaucoma with cannabinoids as hypotensive and neuroprotective agents for the eye (Cairns, Baldridge, & Kelly, 2016).

Anxiety disorders

Although marijuana use has been thought to be associated with a broad range of psychiatric disorders, statistical analysis has shown marijuana use to be associated only with increased prevalence and incidence of alcohol and drug use disorders, including nicotine dependence (Blanco et al., 2016). However, marijuana use among people with anxiety or depression has been reported to be two to eight times higher than in the general population, with rates as high as 60% among people with panic symptoms (Bricker et al., 2007). Several studies suggest that marijuana, self-prescribed and smoked or prescribed in pharmaceutical form, may be effective in treating symptoms related to anxiety; however, a 2015 review of the literature by Vorspan, Mehtelli, Dupuy, Bloch, and Lépine found that marijuana used in self-medication as a sedative can also be a "cause of anxiety disorders" (p. 4).

A review of the literature suggested that, as of 2009, frequent users of marijuana consistently had a high prevalence of anxiety disorders and people suffering from an anxiety disorder have often used marijuana. It was not clear from existing data if marijuana use increased the risk of developing long-lasting anxiety disorders (Crippa et al., 2009). Studies are needed to further understand and test the hypotheses regarding the relationship between anxiety and marijuana, taking into account neurobiological, environmental, and social influences.

One study found that social anxiety is positively associated with marijuana-related problems. Although no significant direct effect of social anxiety on marijuana use frequency was observed, a significant indirect effect on solitary marijuana use was found. This research suggests that social anxiety exerts its influence on marijuana use frequency indirectly via more frequent solitary use. Solitary marijuana use was related to more marijuana-related problems. This finding was congruent with the investigators' previous work, which found that socially anxious marijuana users tended to avoid social situations when marijuana was unavailable. Socially anxious persons used marijuana prior to social events to manage anticipatory anxiety about the event and/or used marijuana following the social event to manage their anxiety associated with review of negative aspects of their behavior during the social event (Buckner, Ecker, & Dean, 2016).

A study of 149 male and female participants, aged 18 to 36, used various statistics to investigate the factors, such as social anxiety, norms, and expectancies, that might go into craving marijuana. The craving was greatest when marijuana use was viewed as acceptable and expected to reduce tension. Cravings due to social anxiety were low when expectations were low. The study found that non-Caucasian participants reported greater tension-reduction expectancies than Caucasian participants. This study suggests the importance of considering social norms, expectancies, and social anxiety in understanding marijuana-related behaviors, given that craving is robustly related to marijuana use problems, such as relapse during an attempt to quit (Foster, Ecker, Zvolensky, & Buckner, 2015).

A meta-analysis included a total of 267 studies on marijuana use in anxiety. The results of 31 of those studies were reanalyzed using a random-effects meta-analysis with inverse variance weights. Analysis of the epidemiological data from the cohort representing 112,000 non-institutionalized members of the general population of 10 countries (the United States, Canada, Switzerland, Australia, France, Colombia, New Zealand, Netherlands, Germany, and the United Kingdom) found a small positive association between anxiety and either marijuana use (Odds ratio [OR] = 1.24, 95% confidence interval [CI], $p = 0.006$; $n = 15$ studies) or marijuana use disorders (OR = 1.68, 95% CI, $p = 0.001$; $n = 13$ studies) and between comorbid anxiety and depression and marijuana use (OR = 1.68, 95% CI, $p = 0.004$; $n = 5$ studies; Kedzior & Laeber, 2014).

A study conducted with 232 participants between the ages of 18 and 70 years who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for panic disorder tested an intervention that included cognitive-behavioral therapy (CBT; six sessions in 3 months followed by six follow-up 15- to 30-minute phone sessions) and marijuana use. Core panic symptoms were assessed using the Anxiety Sensitivity Index, social phobia by the social phobia subscale of the Fear Questionnaire, and depression by the 20-item Center for Epidemiological Studies Depression Scale. Recent marijuana use (smoking) was also recorded. Findings of the study suggested that monthly marijuana use combined with CBT did not significantly reduce anxiety, panic, or social phobia, but it was effective in persons with depression. The investigators noted significant comorbidity between anxiety and depression and suggested that the anxiety arm of the study may not have had sufficient power to detect the effect. The symptoms of persons with depression who smoked marijuana monthly showed no more improvement than the symptoms of persons who smoked less than monthly (Bricker et al., 2007).

Trauma- and stressor-related disorders

Rates of marijuana use have increased in the wake of major disasters. There also are high rates of posttraumatic stress disorder (PTSD) in the United States, particularly in combat-exposed veterans. Marijuana use disorder is associated with PTSD (OR = 4.3). Some researchers hypothesize that individuals with PTSD might benefit from marijuana use. One review of the literature found, however, that the known risks of marijuana outweigh the unknown benefits for PTSD (Steenkamp, Blessing, Galatzer-Levy, Hollahan, & Anderson, 2017). Posttraumatic stress disorder:

> *Symptom severity is positively associated with (a) use of marijuana to cope, (b) marijuana use problems, (c) severity of marijuana withdrawal, and (d) experiences of craving related to compulsivity and emotionality, with findings regarding withdrawal and emotion-related craving remaining significant after adjusting for covariates* (Boden, Babson, Vujanovic, Short, & Bonn-Miller, 2013, p. 277).

Although a range of psychotherapies have been employed with varying degrees of effectiveness, persons who suffer with PTSD may not seek care, and a recent meta-analysis of pharmacotherapy for PTSD found only small effects (Steenkamp et al., 2017).

Depressive and bipolar disorders

A recent survey measured the statistical association between the age at which people first used marijuana and depression in two ways. First, two statistics (linear regressions) used scores from three assessments – the 12-Item Short-Form Health Survey, the Mental Component Summary, and the Major Depression Inventory – as the dependent variables, with the age at first use of marijuana as the independent variable. Second, two regression analyses used age at marijuana first use as the independent variable (with lifetime nonusers as a reference), and poor mental health and major depression as the dependent variables. The results confirmed that marijuana first use at a young age is an important risk factor in the progression to other drug use. Mental health and depression were significantly predicted by age at marijuana first use. However, after controlling for the frequency of marijuana use and for the misuse of alcohol, cigarettes, and other drugs, the association with depression did not persist and the association with poor mental health was reduced. These results underscore the importance of preventing early marijuana users from progressing to other drugs. Among individuals whose first use of marijuana is early in life, these results suggest that the risks of mental health problems and depression are subsequently mediated by abusive consumption of marijuana or other substances. Early onset does not appear to be an indicator of later mental health problems per se, as long as it is not followed by harmful patterns of substance use (Henchoz et al., 2016).

Major depressive disorder is known to be more common in women. Conflicting reports exist concerning the relationship between gender and the prevalence of the use of marijuana to cope with emotional distress. Researchers conducted a secondary analysis of the results of a marijuana intervention trial involving 332 young adult women. Changes in depression symptoms (categorized as minimal, mild, and moderate or more severe depression) were assessed using Beck's Depression Scale in relation to changes in marijuana use at 3 and 6 months after the baseline assessment. The purpose of the study was to examine reduction in marijuana use and its impact on depression symptoms. After controlling for alcohol, investigators found a significant relationship between reductions in marijuana use and reductions in depression symptoms among young women who reported at least some mild depression symptoms (Moitra, Anderson, & Stein, 2016).

Recently, the European Mania in Bipolar Longitudinal Evaluation of Medication study analyzed a sample of 1,922 adults who had experienced a manic/mixed episode of bipolar disorder. Participants' data were organized into three groups: current use of marijuana (between 12-week and 24-month visits), no current but previous use (during first 12 weeks), and never use marijuana. The study found that people with bipolar disorder who stopped using marijuana during their manic/mixed episode had similar clinical and functional outcomes to those who had never used marijuana. People who continued to use marijuana had a higher risk of recurrence and poorer functioning, such as work impairment and not living with a partner. Investigators surmised that the clinical implications of the findings were that a holistic management plan for bipolar patients should include psychoeducation and other treatments/interventions that focus on stopping use of marijuana, alcohol, and other drugs, as well as on improving adherence and preventing relapses (Zorrilla et al., 2015).

Schizophrenia and other psychoses

One of the primary concerns cited in the controversy over decriminalization and legalization of marijuana is its causal relationship with psychosis. Debate is ongoing concerning whether ingesting or smoking marijuana increases the risk for psychosis or, conversely, whether marijuana use contributes to the alleviation of symptoms associated with schizophrenia. Marijuana, while not seeming to cause any basic structural changes in the brain, does appear to make changes in areas of the brain responsible for memory and emotion. Whether these changes are transitory or permanent and whether they contribute to the pathophysiology of schizophrenia are unknown. Many studies now show a robust and consistent association between marijuana consumption and the development of psychosis, but this may not be the case for schizophrenia specifically. Two primary kinds of data inform this issue: studies done with people with schizophrenia and studies of first-episode psychosis. Evidence suggests that the use of marijuana does not in itself cause a psychotic disorder. Rather, the evidence suggests that both early and heavy use of marijuana are more likely in individuals with a vulnerability to psychosis (Ksir & Hart, 2016). Longitudinal studies show a consistent association between adolescent initiation of marijuana use, in a dose-dependent fashion, and the emergence of psychotic symptoms and their severity, along with functional impairment and worse outcomes (Bagot, Milin, & Kaminer, 2015). A study of 64 participants who were followed for 5 years demonstrated that continued marijuana use with subclinical depression symptoms is associated with poorer clinical outcome and may be a predictor of negative outcomes in persons experiencing their first episode of psychosis (González-Ortega et al., 2015). Another study found a dose-dependent association between *change* in marijuana use (from intermittent to continual use) and relapse of psychosis that is not thought to be the result of self-medication or genetic or environmental variables (Schoeler et al., 2016). Such findings are helpful for healthcare professionals, who can test them in practice. For example, a person considering the benefits and risks of marijuana use might be told that a study by Schoeler and colleagues in 2016 found that when users who had experienced psychosis changed from intermittent or occasional use to more continual use, such as smoking marijuana every day, they had a statistically greater risk of psychosis relapse.

According to a Cochrane review (McLoughlin et al., 2014), the evidence from research is unclear concerning a possible relationship between marijuana and schizophrenia. For some people with schizophrenia, positive symptoms are worse when they use marijuana. "For many, however, using marijuana seems only to have the expected mild soporific effects that probably compound negative symptoms" (McLoughlin et al., 2014, p.

41) such as blunted affect, anhedonia, and asociality. Upon reinspection with lead investigators of the studies covered in the Cochrane review on marijuana and schizophrenia, researchers concluded that there was as yet no evidence to demonstrate that one type of adjunct psychological therapy or one type of drug therapy was more effective than another and that there was also insufficient evidence to show that CBD had an antipsychotic effect (Pushpa-Rajah et al., 2015). Alcohol use is known to confound data in studies on psychosis risk related to marijuana use (Auther et al. 2015), as could any substance, such as stimulants. Research also differentiates the amount of marijuana use in self-care as a factor in research outcomes. For example, "heavy" marijuana consumption (defined as smoking more than three marijuana cigarettes per day) seems to impair verbal memory in first-psychotic-episode patients. Heavy users also perform worse than medium users in other neurocognitive tasks. Medium users (one to three "joints" or marijuana cigarettes per day) did not show any greater risk than nonusers. Based on these results, investigators inferred the existence of a dose-related effect of marijuana consumption (Núñez et al., 2015).

Multiple sclerosis and spasticity

Data from more than 40 clinical trials of marijuana and cannabinoids have been published. Beyond the two indications for which dronabinol and nabilone are already approved by the FDA (see Chapter 2), the strongest evidence exists for the use of marijuana and cannabinoids as phytotherapies for chronic pain, neuropathic pain, and spasticity associated with multiple sclerosis. As of March 2015, there had been six trials (n = 325 patients) that examined chronic pain, six trials (n = 396 patients) that investigated neuropathic pain, and 12 trials (n = 1,600 patients) that focused on multiple sclerosis. Several of these trials had positive results, suggesting that marijuana or cannabinoids may be effective therapies. In 2014, the American Academy of Neurology published evidence-based guidelines that recommended an oral marijuana extract containing both THC and CBD (not yet available in the United States as an FDA-approved medication) as having the highest level of empirical support as a treatment for spasticity and pain associated with multiple sclerosis. Synthetic oral THC and Sativex (THC and CBD) oromucosal spray followed with "effective" ratings (Yadav et al., 2014). One systematic review of the literature suggests a clear role for marijuana preparations in symptom management of movement disorders that are known to worsen in people who are anxious. The review found that marijuana in various formulations is effective in reducing symptoms, especially hyperkinetic symptoms, or the anxiety that aggravates symptoms in some conditions (Koppel, 2015).

Cancer and pain management

Cannabinoids have known antineoplastic and antitumor effects (Ramer & Hinz, 2008, as cited in Kendall & Alexander, 2017). Marijuana use is not a new subject for healthcare professionals who care for people being treated for cancer and the discomfort related to the disease and treatments. Nor is it new to those who care for people being treated for chronic and intractable noncancer pain. According to Donald Abrams (2016, p. 404), who has been an oncologist for 35 years and has advised patients about the use of marijuana for some time, "We recommend a self-titrated dosing regimen for the patient as the safest option, rather than attempting to prescribe an actual dose." Dr. Abrams expresses caution in recommending marijuana to older adults because of the plant's ability to lower blood pressure and raise the heart rate. Older adults can experience postural hypotension, leading to falls. He remarks that he has found that his patients generally tolerate the mild euphoria that they feel as an effect of marijuana. Dr. Abrams (2016, p. 404) notes that, "If I have a single medicine that I can recommend to assist with nausea, anorexia, insomnia, depression, and pain rather than prescribing five or six pharmaceuticals that may interact with each other or the patient's chemotherapy, I consider it an attractive option for my patients." This experienced physician takes a pragmatic approach. He understands that a person who has been told to eat only a quarter of a marijuana cookie might then consume the rest of the cookie if his or her pain is not relieved quickly. However, the person may then suffer discomfort from the psychoactive effects of the plant. Helping a person who has had an experience such as this could be compared to guiding the behavior of someone who has been overeating or overexercising to a level of discomfort or injury. Self-care is a vital part of a person's healing process. It is a time when a person learns about his or her own body's needs in new ways. Nurse-scientist Dorothea Orem wrote, "Self-care is not the performance of this act or that act. Self-care requires the seeing of relationships among factors, for example, diet, activity, and insulin in the management of a diabetic condition. It requires the making of adjustments in care actions on a day-to-day basis or more frequently. It requires the incorporation of self-care into the pattern of daily living" (Orem, Renpenning & Taylor, 2003, p. 213). Marijuana self-care compels a period of time spent adapting to its effects and titrating to the right dose as the person incorporates the plant into his or her lifestyle.

Marijuana has also been used extensively by people who suffer from nausea and vomiting during chemotherapy treatment. Cotter (2009) conducted a systematic literature review to evaluate the efficacy of smoked marijuana and THC as treatment for chemotherapy-induced nausea and vomiting (CINV), a well-documented concern. A synthesis of the data in the review shows that marijuana and synthetic oral THC are more effective than placebo in treating CINV from unnamed chemotherapeutic drugs with a high emetic potential. When using traditional oral antiemetics or drugs of a moderate to high potential for CINV, smoked marijuana and oral THC were found to be equally effective. Oral THC and smoked marijuana have similar efficacy, but with smoked marijuana having the additional risk related to inhalation of smoke (Cotter, 2009).

Whiting and colleagues (2015) published a systematic review considering 28 studies involving a total of 2,454 participants and preparations including inhaled marijuana, dronabinol, nabilone, and nabiximols (Sativex; available outside the United States), among others. Twelve of the studies investigated neuropathic pain, and three looked at patients with cancer pain. The studies generally showed improvement in pain measures, with an overall OR of 1.41 (95% CI: 0.99 to 2.00) for improvement in pain with the use of cannabinoids compared with placebo. An earlier systematic review (Lynch & Campbell, 2011) of 18 randomized controlled trials of cannabinoids in 766 participants with chronic noncancer pain found that 15 of the studies reported a significant analgesic effect for the cannabinoids compared with placebo, and a number of the studies also noted improvements in sleep.

Neuropathic pain is also a concern in the care of cancer patients. A systematic review was conducted of the randomized controlled trials involving marijuana and cannabinoids for the treatment of chronic nonmalignant neuropathic pain. Analysis of the 13 included studies showed that cannabinoids may provide effective analgesia in chronic neuropathic pain that is unresponsive to other treatment (Boychuk, Goddard, Maurio, & Orellana, 2015). Another systematic review of six randomized, double-blind, placebo-controlled trials of cannabinoids (five specifically addressing neuropathic pain) found evidence for the use of low-dose medicinal marijuana in refractory neuropathic pain in conjunction with traditional analgesics (Deshpande, Mailis-Gagnon, Zoheiry, & Lakha, 2015). A randomized controlled trial of nabiximols in 359 cancer patients with poorly controlled pain despite a stable opioid regimen found that the

sublingual preparation (4, 10, or 16 sprays daily for 5 weeks) reduced both pain and sleep disruption (Portenoy et al., 2012). A pharmacokinetic interaction study of vaporized marijuana in 21 patients with chronic – mostly noncancer – pain taking sustained-release morphine or sustained-release oxycodone showed no significant effect on plasma levels of the opiates but did suggest enhanced analgesia. The investigators added anecdotal evidence for the decreasing need for opiates when patients began taking marijuana (Abrams, 2016).

In a randomized placebo-controlled trial, Sativex did not show a statistically significant improvement in symptoms in those with intractable diabetic peripheral neuropathy pain. Participants were divided into those with and without a history of depression because people with depression have higher baseline pain scores. This study had a large placebo effect, possibly accounting for the failure to show differences between experimental and control groups (Selvarajah, Ghandi, Emery, & Tesgaye, 2010).

A systematic review performed by Fitzcharles, Baerwald, Ablin, and Hauser in 2016 concluded that the finding that cannabinoids are superior to placebo in reducing chronic pain was valid only for neuropathic pain. The evidence for efficacy of cannabinoids reducing pain in people diagnosed with fibromyalgia syndrome (FMS) is inconsistent. However, many people with FMS do seem to think that marijuana is effective. In a study conducted by the U.S. National Pain Foundation, more than 1,339 people with FMS rated marijuana more effective than FDA-approved duloxetine, milnacipran, and pregabalin. The survey showed that only 8% of duloxetine users, 10% of pregabalin users, and 10% of milnacipran users found the prescribed medication to be "very effective," while 60% of duloxetine users, 61% of pregabalin users, and 68% of milnacipran users replied that the medications "do not help at all." In contrast, 62% of marijuana users rated the plant "very effective." Only 5% said that marijuana did not help at all (Fitzcharles et al., 2016).

MRSA and antibacterial action

Methicillin-resistant *Staphylococcus aureus* (MRSA) is an antibiotic-resistant gram-positive bacteria. Studies show that about one in three people in the United States carry *S. aureus* in their noses, usually without any signs of illness, and two in 100 people carry MRSA (Centers for Disease Control and Prevention, 2017). Terpenoids are aromatic compounds found in the essential oil molecules of plants that can act as a part of the broader immune response of a plant; they may be a protectant for a plant against a predator or an attractant for pollinators. Current research on the terpenoids in marijuana, such as alpha-pinene and limonene, could be explored to see if they, like the alpha-pinene in *Sideritis erythrantha* essential oil, are effective against MRSA and other antibiotic-resistant bacterial strains (Köse, Deniz, Sarikurkcu, Aktas, & Yavuz, 2010). Pure CBD powerfully inhibits MRSA (minimum inhibitory concentration 0.5 to 2 mg/mL; Appendino et al., 2008). The ability of monoterpenoids to enhance skin permeability and entry of other drugs may further increase antibiotic benefits (Russo, 2011).

A study tested hemp seed oil, as well as its emulsion, against the growth of selected bacteria using disk diffusion and broth microdilution methods. The antibacterial effect of hemp seed oil was documented against *Micrococcus luteus, Staphylococcus aureus* subsp. Aureus, and *Salmonella.* Oil quality depends on seed origin and extraction method. The formulated emulsions did not exhibit the anticipated antibacterial activity. However, unrefined cold-pressed hemp seed oil did show activity (Mikulcová, Kašpárková, Humpoliček, & Buňková, 2017).

Marijuana for other diseases and health concerns

Researchers are examining marijuana's role in the relief of symptoms related to a number of disease and health concerns. The following are a few examples of published studies.

Crohn's disease

Anecdotally, people have reported marijuana as having a positive effect on Crohn's disease symptoms. In one study (Naftali et al., 2013), the sample size was 21 patients (mean age 40 years ± 14 years; 13 men) with Crohn's Disease Activity Index (CDAI) scores greater than 200/600 (disease severity) who had not responded to therapy with steroids, immunomodulators, or antitumor necrosis factor-alpha agents. Patients were assigned randomly to two groups, one given marijuana cigarettes containing 115 mg of THC twice daily and the other given cigarettes containing marijuana flowers from which the THC had been extracted. Disease activity and laboratory tests were assessed during 8 weeks of treatment and then 2 weeks thereafter. Complete remission (CDAI score < 150) was achieved by 5 of 11 subjects in the marijuana group (45%) and 1 of 10 in the placebo group (10%; $p = 0.43$). A clinical response (decrease in CDAI score of >100) was observed in 10 of 11 subjects in the marijuana cigarettes group (90%; from 330 ± 105 to 152 ± 109) and 4 of 10 in the placebo group (40%; from 373 ± 94 to 306 ± 143; $p = 0.028$). Three patients in the marijuana group were weaned from steroid dependency. Subjects receiving marijuana cigarettes reported improved appetite and sleep, with no significant side effects. Although the primary end point of the study (induction of remission) was not achieved, a short course (8 weeks) of THC-rich marijuana produced significant clinical, steroid-free benefits in 10 of 11 people with active Crohn's disease as compared with those who received placebo, without side effects. Although this study had a small sample, the attention given to the botanical detail of the study design is superior. The investigators acknowledged and accounted for the problem that medicinal marijuana and all plants contain various constituents in a mixture, making it difficult to measure the contribution of each one. They dealt with the standardization issue by choosing marijuana for the study from genetically identical plants grown from twigs of the same mother plant and in equal conditions. Plants were tested to verify an equal content of active ingredients. The investigators also standardized the machine-made cigarettes to contain equal weights of marijuana flowers (Naftali et al., 2013).

Nonalcoholic fatty liver disease

A population-based, case-controlled correlational study tested the hypothesis that marijuana is associated with reduction in nonalcoholic fatty liver disease. The risk factors identified from more than 6 million patient records included age 40 to 60 years, being female, hyperlipidemia, hypertension, alcohol use, diabetes, metabolic syndrome, and being a non-Hispanic White person. The study found the hypothesis to be supported (Adejumo et al., 2017).

AIDS-associated anorexia

According to Lutge, Gray, and Siegfried (2013), the FDA approved dronabinol for the treatment of AIDS-associated anorexia using a study published in 1995 that at the time was the only study amenable to further analysis. The study, with a sample size of 139 (88 evaluable), found that participants administered dronabinol were twice as likely to gain 2 kg or more in body weight. The mean weight gain was 0.1 kg, as compared to a loss of 0.4 kg in the placebo group.

Sleep disturbances

Sleep disturbances are prominent symptoms in individuals with substance use disorders. A self-report online survey of 248 people suggests that those who are "risky" marijuana and/or alcohol users are likely to report poor sleep quality rather than daytime sleepiness. Riskiness was determined by a score of lower than 6 for a 39-item instrument called the Marijuana Screening Inventory. Women typically have poorer sleep outcomes than men, as do people who use both alcohol and marijuana (Ogeil, Phillips, Rajaratnam, & Broadbear, 2015).

A study of 13 daily marijuana users, all men, examined the effects of around-the-clock dosing with oral THC on sleep latency and ability to fall asleep. The participants were given an escalating dose up to 120 mg on days 5 and 6. The overall amount of nighttime sleep decreased slightly during the study. Although other reports have suggested that people typically have somnolent side effects after receiving oral THC, this study suggests, although it had a very small number of participants, that people may become tolerant to the effects of THC through sustained use (Gorelick et al., 2013).

Rapid eye movement sleep behavior disorder (RBD), in which people act out their dreams, is considered a prodromal symptom of Parkinson's disease (PD). Marijuana is being explored for its neuroprotective effects in RBD/PD. Four patients with RBD/PD were treated with CBD for 6 weeks. Three received 75 mg per day and one person 300 mg per day. All four subjects had a significant decrease in symptoms (Chagas et al., 2014).

Conclusion

Clinical research evidence on marijuana's use in the treatment and care of disease is limited. Thousands of peer-reviewed papers on marijuana have been written, and many are literature reviews and meta-analyses of research performed around the globe. However, the illegal status of marijuana in the United States (discussed further in Chapter 4) implemented with the 1937 Marijuana Tax Act virtually terminated all research on marijuana in the United States. This status poses an ongoing challenge to researchers interested in conducting the clinical trials demanded by the public and professionals alike.

In the meantime, extensive population studies have been conducted that provide some insight into the effects of marijuana use. For example, a systematic review and meta-analysis found in a review of 79 trials (6,462 participants) that there is evidence of moderate quality to support marijuana treatment of chronic pain and spasticity. Research has also found that evidence for the long-held belief that marijuana can be of use in treating the nausea and vomiting often associated with cancer chemotherapy is of low quality (Whiting et al., 2015), and yet the only FDA-approved drugs derived from marijuana are approved for that purpose.

Laboratory studies that analyze plant constituents in marijuana, such as THC and CBD (see Chapter 2), have led to the beginning of drug development in the hope of cures and greater comfort. Research is still inhibited by legal status, politicization, and social stigma, given the history of marijuana's use as a self-prescribed drug for intoxication as well as medication. However, this chapter has described research that, though limited, shows promise in many areas of human health, from chronic pain management to resolving MRSA infection to easing epilepsy. The final chapters, 4 and 5, will focus on the benefits and risks to public health and the significant number of behavioral and social issues that come with the legalization that now seems almost inevitable. Healthcare professionals who maintain knowledge of the subject and communicate with their patients who use marijuana can support the transition from stigma to science to translation, where evidence informs person-centered assessments and clinical decision making.

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CHAPTER 4: LEGAL STATUS AND TREATMENT

Marijuana is the most commonly used illicit drug in the United States. In one month in 2014, as reported by the Substance Abuse and Mental Health Services Administration (SAMHSA), more than 22 million people aged 12 years and older used marijuana. According to the 2014 survey, 4.2 million people had disorders related to the use of marijuana. Among adolescents aged 12 to 17, 2.7%, or 667,000, were found to have marijuana use disorder (SAMHSA, 2015).

Now that the use of marijuana is becoming legal in many states, registered nurses, advanced practice nurses, pharmacists, and behavioral healthcare providers are well positioned to affect the choices communities make about the supply, distribution, prescription, and care of people using marijuana, as well as the regulatory developments surrounding marijuana's future, its use, and abuse. Worldwide, the growing development of marijuana-based medicines has led to greater discussion among prescribers, the public, and policy makers. Ethical principles in health care mandate a degree of separation between the prescribing of a drug and its supply, thus necessitating the need for independent channels of distribution. In the case of marijuana, growers are engaged in distribution and quality control of supply, and marijuana dispensaries are being established in states where marijuana is legal. Should the federal prohibition on marijuana be lifted and medical marijuana be legalized, pharmacists may also be responsible for the handling, supply, counsel, and oversight of the safe use of the plant as well as its related products and drugs. This chapter highlights the current status of marijuana legalization and perhaps one of the biggest challenges of marijuana legalization: treatment planning for the projected potential increase in marijuana dependence and substance misuse.

LEGALIZATION STATUS

The line between medicinal and recreational use of marijuana is often blurred. Greater awareness and education can clarify distinctions between these two purposes for using marijuana (Isaac, Saini, & Chaar, 2016). Chapter 1 of this course provided insight into the cultural and historical context of both medicinal and recreational uses. Marijuana's legal status has often been contrasted with that of legal opioids, which have killed thousands more people than marijuana. (States that have legalized marijuana have reported a substantial decline in opiate and pain medication prescription overdose rates; Schepker, 2017). Use of both illicit and prescription opioids has reached the status of a "public health emergency" (U.S. Department of Health and Human Services, 2017). This is not to say that there are not significant potential risks in the legalization of marijuana. A published review of drug policy publications suggests that it is plausible that legalizing recreational marijuana use in the United States could substantially reduce its price and increase heavy use and marijuana-related problems such as dependence and substance misuse among those who already use the drug. In the longer term, legalization may also increase the number of new users (Hall & Lynskey, 2016).

To provide background to the issue of legalization of marijuana, the following is a brief outline of the history:

- **1850:** In the United States, marijuana was sold over the counter and was commonly used as treatment for such diseases as cholera, alcoholism, opiate addiction, and convulsive disorders.
- **1906:** Congress passed the Pure Food and Drug Act, a piece of legislation designed to restrain abuses in the patent-medicine industry. It was also the first piece of legislation in the United States to mention marijuana. Until this time, there was no concerted effort on the part of the government to regulate psychoactive substances. Cocaine was still in Coca-Cola; heroin kits were available for sale at Sears. No drug was illegal.
- **1930:** The Federal Bureau of Narcotics (FBN) was formed in Washington, D.C.
- **1936:** Every state then in the union passed a law restricting possession of marijuana and eliminating its availability as an over-the-counter drug.
- **1937:** Although opposed by the American Medical Association, the Marihuana Tax Act of 1937 was passed to prohibit all nonmedical use of marijuana in the United States. However, the law also limited medical use with fees and regulatory restrictions that imposed a significant burden on physicians prescribing marijuana.
- **1970:** On October 27, 1970, the Comprehensive Drug Abuse Prevention and Control Act was enacted. Title II of the act – The Controlled Substances Act – established categories varying from Schedule I (the strictest classification) to Schedule V (the least strict). Marijuana was placed in the Schedule I category, thereby prohibiting its use for any purpose.
- **1996:** California voters approved Proposition 215 to legalize medical marijuana. However, the Clinton Administration opposed the proposition and threatened to revoke the prescription-writing privileges of doctors who prescribed the drug. Since the passage of Proposition 215, marijuana use among youth in California has declined significantly (Lee, 2012).

Although the federal government of the United States currently prohibits the sale and use of marijuana, eight U.S. states and the nation's capital have made marijuana legal for all adults, and most states allow for some use of medicinal marijuana. A total of 29 states, the District of Columbia, Guam, and Puerto Rico allow for comprehensive public medicinal marijuana programs. The Marijuana Policy Project (2018) and the National Conference of State Legislatures (2017) provide web-based resources that detail each state's legalization status for medicinal marijuana. Contained within the federal budget are provisions to protect a state's right to responsibly regulate medical marijuana programs. Since December 2014, the Rohrabacher-Farr amendment has prohibited the Justice Department from spending funds to interfere with the implementation of state medical marijuana laws. This amendment must be renewed each fiscal year to remain in effect and was included in a series of spending bills approved in 2016 and 2017, with the most recent extension being approved with the passage of the budget on February 9, 2018. Several states and the District of Columbia have stopped

jailing individuals for possession of small amounts of marijuana (Marijuana Policy Project, 2017).

Despite concerns that legalization of marijuana could increase crime risk, several studies have shown that instating laws allowing for medical marijuana and dispensaries is not associated with increased crime. In 2012, a study published in the *Journal of Studies on Alcohol and Drugs* found that the density of medical marijuana dispensaries was not associated with violent or property crime rates (Kepple & Freisthler, 2012). In 1914, the Harrison Act placed narcotics under the regulatory control of the federal government, restricting access to nonmedical consumers. The Harrison Act made the first legal distinction between recreational and medical use of drugs. That year, undercover sting operations led to the arrest of 25,000 physicians on narcotics charges. Three thousand were given prison sentences and "thousands had their licenses revoked for giving out opiates" (Lee, 2012, p. 41). The pharmaceutical industry's lobby did, however, keep marijuana from being covered by the Harrison Act. Few people were smoking marijuana at the time, although some were still eating hashish. Prohibition of marijuana began in California, where it was outlawed in 1915. The political rationale was control of Mexicans in the labor force. "Arrests and convictions of 'Mexican' workers for marijuana possession were most concentrated during the years of, and in the areas with, the highest levels of labor organization and action" (Lee, 2012, p. 42). During most of the Prohibition era, marijuana was exempt from national crime legislation; however, in 1929 Congress passed the Narcotic Farms Act (later repealed in 1944), which misclassified Indian hemp as a habit-forming narcotic (Lee, 2012) and authorized construction of two hospitals in the prison system for treating drug addicts, including nonmedical marijuana users deemed addicts (Lee, 2012). As a social upside, marijuana was at the center of the jazz culture that brought together Black and White Americans interested in the emerging music genre. By 1931, when the FBN was formed in Washington, D.C., many states had banned marijuana.

Marijuana is currently listed as a Schedule I substance under the Controlled Substances Act of 1970, the highest classification under the legislation, and remains illegal *at the federal level.* The Controlled Substances Act regulates the manufacture, importation, possession, use, and distribution of substances such as marijuana. A Schedule I drug, as defined by the U.S. Drug Enforcement Administration (DEA), is a substance that has a high potential of being abused by its users and has no acceptable medical use (DEA, n.d.). Recently, however, legislation has been rapidly changing at the state level. Health professionals, along with the public and legislators, are reviewing the evidence resulting from marijuana prohibition. Some evidence suggests that marijuana laws have contributed to increased prevalence of illicit marijuana use and marijuana use disorders (Hasin et al., 2017). States recognize (make the policy for) medical use, limited medical use, no access laws, or some recreational use.

State requirements and healthcare professionals' role with regard to "medical marijuana"

State-by-state requirements related to healthcare professionals' interactions with marijuana for "medical" purposes are as varied as the states' laws and educational programs on the topic. Advanced practice nurse prescribers, nurses, pharmacists, and behavioral healthcare professionals are required in some states to have continuing education on the subject. Other states require people who prescribe or work in dispensing facilities to complete state-approved courses. The following is an example from the state of Colorado, the first state to legalize recreational and medical use of marijuana, considered a potential prototype for legalization and associated social policy development in other states.

Colorado as an example of what healthcare professionals might need to know

The state of Colorado has a "registry" for those who engage with medicinal marijuana for any purpose (Colorado Department of Public Health & Environment, 2018). Physicians are registered separately from "caregivers." Colorado Revised Statute 25-1.5-106 (LexisNexis, n.d.) defines four types of caregivers, the services they provide, and legal requirements as indicated in Table 4-1.

According to the Colorado Medical Marijuana Registry website, the first step when seeking to be added to the registry is to check eligibility. To be a "caregiver" in Colorado, a person must meet the qualifications of:

- Age 18 or older.
- Colorado resident.
- Not the patient's physician.
- Not have one's own primary caregiver (as defined in Table 4-1).
- Not licensed as a medical marijuana business.

State law allows "cultivating caregivers" to grow up to 99 plants for medical marijuana patients. If caregivers cultivate more than 99 plants, they are required to register with the Department of Revenue (DOR) as a licensed business. (A licensed medical marijuana business cannot also register as a primary caregiver.) Caregivers must register the address of all cultivation and transportation locations with the DOR along with the number of patients and the plant/ounce count (amount of marijuana) associated with each address.

Patients are allowed to cultivate the number of plants recommended by a physician; however, in 2015 the governor of Colorado signed Senate Bill 15-014 into law (Colorado State Legislature, 2015). This law limits patients to cultivating no more than 99 plants. Patients cultivating above the standard six plants/2 ounces are encouraged, but not required, to register with the Department of Revenue's caregiver registry.

An adult patient's cultivation options are listed below:

- Patients can cultivate all of their medical marijuana themselves.
- Patients can cultivate a portion themselves and have a caregiver cultivate the rest.
- Patients can cultivate a portion themselves and have a center cultivate the rest. A Medical Marijuana Center registers as a business with the State of Colorado Department of Revenue's Marijuana Enforcement Division (Colorado Department of Revenue, 2018).
- Patients can have a caregiver cultivate all of their medical marijuana.
- Patients can have a center cultivate all of their medical marijuana.

Additionally, it is not only in relationships with the public that healthcare professionals must be conscious of federal and state law regarding marijuana use. A Colorado Supreme Court case addressed this issue when an employer fired an employee who had used medical marijuana legally. The employer argued that it was complying with federal law, and in particular it was obligated to comply with the "Drug-Free Workplace Act because it was a federal contractor. The Supreme Court ruled in favor of the company, saying that with an obvious conflict between state and federal laws, the employer can take the more conservative position of complying with federal law" (Relias [AHC Media], 2017). In summary, anyone providing professional advice or education about medical marijuana must know federal and state law and the parameters of the prescription for the individuals they are choosing to help.

Table 4-1: Legalized Medicinal Marijuana: Designated Caregivers	
Cultivating	Grows marijuana on behalf of patients.
Transporting	Transports marijuana for homebound or minor patients.
Parents of a minor patient	Parents of a patient under the age of 18.
Advising	Advises patients on the medicinal use of marijuana. *Note:* Advanced practice nurses, nurses, pharmacists, and behavioral healthcare professionals are not included in this category. The category includes only practitioners who do advising work in dispensaries. The statute is currently silent on other roles.

Note. Adapted from LexisNexis. (n.d.). Colorado legal resources. Retrieved from https://advance.lexis.com/container?config=0-345494EJAA5ZjE0MDIyYy1kNzZ-kLTRkNzktYTkxMS04YmJhNjBlNWUwYzYKAFBvZENhdGFsb2e4CaPI4ck6laXLCWyLBO9&crid=9f9087ad-a2bb-4b2f-b82b-74-19ccd058e9&prid=376ea9de-0cdc-4c28-9195-dd2fcd553489.

TREATMENT FOR MARIJUANA DEPENDENCE AND CESSATION

Regardless of whether a substance is legal or illegal (and because of competing state and federal laws, marijuana is often both), people can develop a dependence. Among the problems of dependence is that a person who attempts to change his or her behavior can experience withdrawal. Common symptoms of withdrawal from marijuana in humans include:

- Anger and aggression.
- Anxiety.
- Depressed mood.
- Irritability.
- Restlessness.
- Sleep difficulty and strange dreams.
- Decreased appetite and weight loss.
- Headaches.
- Stomach pain.

(Vandrey & Haney, 2009)

Symptoms typically last 1 or 2 weeks (Vandrey & Haney, 2009). Possibly because of marijuana's historically illegal status, the literature is scant on any one treatment targeted specifically at marijuana dependence. However, a brief overview of some of the studies that have been conducted for treatment and dependence are included here. It is beyond the scope and purpose of this course on medicinal marijuana to delve too far into the subject of substance use disorders and treatment strategies or the trauma exposure commonly underlying substance use and misuse. The focus here is specific to marijuana and the clinical research evidence base that is developing and that perhaps has shown some promise. Therapy work is particularly complicated in young people due to the drug culture that surrounds them. They may not be motivated to commit to marijuana cessation treatments that focus exclusively on reducing drug use as the goal. Screening for and treating the problems that are meaningful to them are thought to be the best approach to increasing treatment relevance, motivation, and commitment (Shane, Diamond, Mensinger, Shera, & Wintersteen, 2006).

Screening for problematic marijuana use

Screening instruments commonly employed in assessing marijuana-related problems – because they are brief and easy to use – are the Severity of Dependence Scale (SDS – symptoms of dependence), Cannabis Use Disorders Identification Test (CUDIT – motivational aspects of use), Cannabis Abuse Screening Test (CAST – social and health problems), and Problematic Use of Marijuana (PUM). All scales have shown moderate to high internal consistency (Cronbach's alpha ranging from 0.72 to 0.92), which means that the scales are good at measuring what they are supposed to measure. The SDS is a five-item scale that measures the degree of psychological dependence, that is, the individual's feeling of impaired control and anxiety toward drug taking. The CUDIT screens for current marijuana use disorders (abuse or dependence), whereas the PUM measures harmful use, problems in interpersonal relationships, and psychophysical functioning. Basically designed for adolescents or young adults, the CAST identifies patterns of marijuana use leading to social or health problems for the user or others in society (Piontek, Kraus, & Klempova, 2008).

Pharmaceutical treatment

Marijuana causes dependence (i.e., feeling symptoms of withdrawal when not taking the drug) in a small percentage of users; however, the knowledge that millions of Americans are using marijuana can compel communities to ask what medications might be effective in treating dependence should it happen. Several medications have been investigated for reducing symptoms of intoxication, withdrawal, and dependence. Norstrom and Levin (2007) provide a detailed summary of trials conducted in the early part of the century. Cannabidiol (CBD) or CBD-rich marijuana itself are known to help chronic marijuana users wean themselves from delta-9-tetrahydrocannabinol habituation. Medications studied have included those known to be effective in the treatment of other drug use disorders, as well as those that alleviate symptoms of marijuana withdrawal or directly affect endogenous cannabinoid receptor function. Results from laboratory studies and small-sample clinical studies indicate that buspirone, dronabinol, fluoxetine, lithium, and lofexidine may have therapeutic benefit. Dronabinol (10 mg, five times daily, for 6 days) is the medication regimen that has shown potential in marijuana withdrawal. The drug decreases cravings, anxiety, chills, and sleep disturbance (Vandrey & Haney, 2009). In a follow-up study, 20 mg, three times daily, for 8 days, was prescribed; however, in this case a significant increase in participants' irritability and sleep disorders was observed.

Residential treatment

A review of 36 articles on outpatient and residential treatment for marijuana dependence included measurement of the relationship between marijuana withdrawal and sleep. The investigators found that existing studies failed to control for confounding variables, such as other substance or medication use and common pre-existing sleep-affecting conditions, such as chronic pain and depression. Participants commonly reported experiencing "trouble sleeping" (41.5% of participants on average), "strange dreams" (34.4%), and "waking up early" (33.2%), whereas "sleeping more than usual" was less common (10.9%). The specific mechanisms by which sleep is affected during marijuana withdrawal are unclear (Gates, Albertella, & Copeland, 2016).

Another study assessed withdrawal in 29 men admitted for 30 days of residential treatment. The investigators concluded that,

measured with a visual analogue scale, the results reflect that marijuana withdrawal symptoms were primarily psychological or sensory. This result was compared with the physical symptoms reported most during the first 3 days of treatment, when the residual physical effects of marijuana (rather than withdrawal symptoms) were greatest. These effects included cravings, hunger, thirst, and feeling "mellow" (Lee et al., 2014).

Outpatient therapy

Gates, Sabioni, Copeland, Le Foll, and Gowing (2016) conducted a review of 23 randomized controlled trials involving 4,045 participants. Fifteen of the studies took place in the United States. The evidence consistently supported the use of cognitive-behavioral therapy (CBT) conducted as individual and group sessions, individual motivational enhancement therapy (MET), and the combination of CBT and MET, for reducing frequency of marijuana use when compared with no treatment. High-intensity interventions of more than four sessions and those delivered over a period of longer than 1 month – particularly MET with CBT interventions – were most effective. No particular intervention was consistently effective at 9-month follow-up or later. In addition, data from five out of six studies supported adding voucher-based incentives for marijuana-negative urine tests to enhance treatment. One study found contrasting results that, throughout a 12-month follow-up period, CBT alone without the addition of abstinence-based or treatment-adherence-based contingency management was most effective in reducing marijuana use. Drug counseling, social support, relapse prevention, and mindfulness meditation were not shown to be as effective in this review because identified studies were few, information on treatment outcomes was insufficient, and the rates of treatment adherence were low (Gates, Sabioni, et al., 2016).

A 10-week outpatient treatment combining mindfulness-based training techniques with supportive psychotherapy was shown to be effective in the treatment of marijuana dependence. Mindfulness is defined as "capacity to attend to phenomena on a moment-to-moment basis, non-judgmentally, and with accepting, relaxed awareness" (Dakwar & Levin, 2013, p. 521). In this study, training included standardized mindfulness-based stress reduction exercises, such as the Raisin Exercise, a centering meditation exercise in which a participant approaches a single raisin using all sensory modalities with the intention of experiencing the raisin for the first time to cultivate a sense of "newness" of the object of attention. The behaviors associated with marijuana use can become habitual and therefore mindless; hence the possibility of addressing dependence first and foremost when quelling habitual mindless behavior. For example, one participant "began to spend greater time in sessions reflecting on the thoughts, perspectives and patterns of behavior that had compromised her quality of life in the past; she also expressed feeling a greater distance and freedom from them" (Dakwar & Levin, 2013, p. 524).

Family therapy can be a helpful service, particularly for adolescent marijuana users. One study found that family therapy is most likely used by unemployed, white male and female adolescents living in urban areas who are heavy marijuana users with a history of prior admissions and who also have a comorbid condition. Findings suggest that family therapy is not best used as a preventative intervention but instead as an intermediate level of treatment or for secondary prevention of serious problems. The findings also suggest that significant barriers to access exist for the families of adolescent marijuana users who seek family therapy (Smith, Malespin, Pereira, & Richards, 2016).

The premise behind acceptance and commitment therapy (ACT) explains substance use problems as an attempt to regulate thoughts, feelings, or other private experiences through substance use, as a form of emotional avoidance (Gundy, Woidneck, Pratt, Christian, & Twohig, 2011). Other aspects of substance use disorders are physiological dependence and internal components such as expectancies and beliefs related to the substance, cravings, bodily sensations, and distressing emotions. Attempts to regulate internal experiences include avoidant, irrational, and emotional coping strategies, such as thought replacement, positive self-talk, hopeful thinking, and distraction. These strategies themselves can cause psychological distress. Proponents of ACT propose that these ineffective coping strategies (avoidance and emotional regulation and detachment), along with beliefs that one lacks control over threatening events, are component processes of a broader construct referred to as experiential avoidance (Gundy et al., 2011). People engage in experiential avoidance in an attempt to avoid unwanted internal experiences, as well as to control or regulate their form, frequency, or situational sensitivity, even when doing so causes harm.

Relatively recently, acceptance and mindfulness-based treatments have begun to emerge as alternative methods to address inner experiences. In mindfulness-based cognitive therapy, attempts are made not so much to change the content of thoughts as to make people more aware of their thoughts, feelings, and bodily sensations. ACT accomplishes this by focusing on a set of core principles that develop psychological flexibility, or the ability to adapt to situations with awareness, openness, and focus, and to take effective action, guided by values. This therapy seeks, therefore, not to eliminate pain or even necessarily to reduce painful psychological symptoms, but rather to decrease their functional impact, thereby allowing changes in the way one lives. To that end, ACT employs a six-step process, consisting of:

- Defusion (understanding passing thoughts and feelings).
- Acceptance.
- Contact with the present moment.
- Self as context.
- Values.
- Committed action.

(Gundy et al., 2011)

"Self as context" means that a person views the self as being separate from and observant of the "content" of the inner experiences (Dewane, 2008).

Twohig, Shoenberger, and Hayes (2007) tested the effectiveness of ACT in marijuana dependence in a multiple-baseline-across-participants design with three adults. The treatment was delivered in eight 90-minute individual sessions with self-reported marijuana use as the main dependent variable and these self-reports confirmed with oral swabbing. Results showed that all three individuals had ceased marijuana usage by post-treatment, and that, at 3-month follow-up, one participant was not using marijuana, one was using significantly less, and one had returned to baseline levels of usage. The results of this study are preliminary.

Community-based activities and programs

One study of 84 marijuana-dependent military veterans in a self-report and self-guided cessation program found that increasing low- and high-level physical activity can be useful during an attempt at cessation (Irons, Babson, Bergeria, & Bonn-Miller, 2014).

Many adolescents receive mentoring to prevent drug abuse (Thomas, Lorenzetti, & Spragins, 2011). A Cochrane review of 233 articles produced four randomized controlled trials conducted in the United States (1,194 adolescents aged 9 to 16 years) that met inclusion criteria. All four described the use of structured mentoring programs as opposed to informal mentors in programs aimed to prevent drug and alcohol use. Two programs used the Across Ages mentoring program, one used the Big Brothers Big Sisters program, and the fourth was a program for adolescents whose parents were HIV-positive. None of the participants were using drugs or alcohol when the studies were initiated. Two of the four studies found that mentoring reduced initiation of alcohol,

and one reduced drug initiation. Unfortunately, however, the measurement of change was difficult to calculate in all studies because the baseline for use was very low (Thomas, Lorenzetti, & Spragins, 2011).

A Cochrane review of 51 studies included 127,146 participants in school marijuana prevention programs. Study programs were mainly delivered in sixth- and seventh-grade pupils. Most of the trials were conducted in the United States. School programs based on a combination of social competence and social influence approaches showed, on average, small but consistent protective effects in preventing drug use, even if some outcomes did not show statistical significance. Social competence curricula address the belief that children learn drug use by modeling, imitation, and reinforcement, which are further influenced by a child's perceptions, attitudes, and skills. These programs teach self-care and social skills such as goal setting, problem solving, and decision making, as well as coping and stress reduction skills. This approach can be compared with a knowledge-focused curriculum in which children are simply given information about drugs with the expectation that knowledge will translate to behavior change (Faggiano, Minozzi, Versino, & Buscemi, 2014).

Case study 4-1: Healthcare professionals' role

Mr. Wallace calls your health, therapy, and pharmacy telehealth service in Denver, Colorado. You are licensed to provide services in Colorado. Mr. Wallace was a construction worker for 25 years. Now in his 40s, he is concerned that his back pain is getting more severe with time. He recently lost 20 pounds and tries to be in bed for at least 8 hours each night, though the pain usually keeps him from sleeping more than 5 hours a night. Over time, he has come to rely more on his prescription for hydrocodone and tells you that he is concerned about addiction to his pain pills. His friends are suggesting marijuana for the pain. He asks you what you think and whether he should consider smoking marijuana or ask for a prescription from his healthcare provider.

Questions

1. How would you approach Mr. Wallace's concern about marijuana use?
2. What is the clinical evidence, if any, supporting the possible use of marijuana for chronic pain?
3. Should Mr. Wallace smoke, get a prescription for marijuana, or neither?
4. What are the legal ramifications of your consultation, if any?

Answers

1. Start by identifying what Mr. Wallace already knows about his options. Listen carefully and then create a plan for weighing the benefits and risks of each option. Ask Mr. Wallace what kind of information and resources he will need to make and then implement a plan that will deal with his pain.
2. There is some research evidence to support the use of marijuana treatment in people with chronic pain, particularly those with neuropathic pain versus other types of pain, such as fibromyalgia pain. Ask Mr. Wallace if he has a pain diagnosis so that you can determine whether to share any relevant study results with him. Many people partner with marijuana for chronic pain. Keep communication open and be willing to participate in a shared decision-making process with Mr. Wallace.
3. Discuss the differences between smoking and other ways of using marijuana. Consider CBD oil, which may help with pain and sleep. Marijuana is still illegal in all states (by federal law), and therefore no prescriber can prescribe marijuana. In states where marijuana is legal (by state law), such as Colorado, prescribers can recommend marijuana or join a registry to be able to provide recommendations that their patients can then take to legal dispensaries that require a prescriber's authorization to dispense marijuana for a specific medical purpose. Help Mr. Wallace register with the Colorado state marijuana registry should he choose to take marijuana or any related product, including CBD oil, which is also illegal according to federal law.
4. Marijuana and related products are illegal under federal law in the United States. In states where marijuana is legal, the healthcare professional's role is one of education and recommendation. Some states may choose to refer to the prescriber's roles as "prescription," but Colorado physicians decided to use the term "recommendation." In states where marijuana is illegal, healthcare professionals may be aiding in the commission of a crime should they participate in any act surrounding the use of marijuana.

Conclusion

The ongoing sociopolitical controversy surrounding marijuana legalization has a negative effect on the ability to conduct clinical research. It also creates challenges in the open promotion and development of treatment techniques and management programs that may be unique to the needs of marijuana users. Public health systems and policies are in place to assist the public and caregivers in the best health decision making to manage community risk and promote health benefits over time. The need for evidence of previously successful treatment of persons with marijuana use disorders is helpful in community planning. The current research on marijuana treatment programs seems to suggest to healthcare professionals the need to address underlying personal and sociocultural issues that may lead an individual to use marijuana in the first place, rather than attempt to implement programs that repress drug-seeking behavior. Illicit drug use prevention in children and youth is of major importance to the future of the nation. One of the first steps healthcare professionals can take in contributing to the body of scientific knowledge and clinical practice experience regarding the use of medicinal marijuana is to study their states' guidelines for practice. In the future, prescribing or recommending marijuana may require registration with the state and specific educational training.

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CHAPTER 5: COMMUNITY HEALTH AND EDUCATION: CONSIDERATIONS AND CONCERNS

No single constituent determines the risks to public health from illicit marijuana use or misuse of medicinal marijuana. Apples, after all, are not removed from the market or banned from farms because the seeds contain cyanide. The risk is weighed against the benefit, which is often a matter of degree. The people and their state legislatures seem to be weighing risks against benefits as, one by one, states are voting to legalize marijuana in varying degrees after decades of prohibition. This chapter focuses on community health and education considerations and concerns related to the growth of the marijuana industry in American communities. When weighing the benefits and risks of using marijuana, some basic questions arise that are relevant to healthcare professionals as represented in professional white papers, position statements, and scientific discussions and publications:

- What do people who use marijuana in their self-care practices need in order to do so safely?
- What is the new role of government in protecting the public if it abandons marijuana prohibition?
- What are the roles and responsibilities of healthcare professionals related to marijuana use?
- What are emerging issues in states that have legalized marijuana related to widespread use?

It is important to consider some of the identified health considerations and concerns related to the growth of the marijuana industry in American communities. In general, healthcare professionals' approach to shared decision making and person-centered care suggests that they will take a client's personal experience into account (see Table 5-1). People have various reasons for choosing their self-care practices. Research has shown that they are often quite rational in their thought processes concerning their health choices, even when they seem to be making choices "alternative" to mainstream biomedical culture's view of safe and effective care (O'Connor, 1995). They may request further information, but such requests should not be interpreted necessarily as a sign of ignorance. The medicinal marijuana culture is a dominant subculture of the larger self-care culture, identified by social scientists as the "hidden health care system" (Levin & Idler, 2010). Medicinal plants have been part of the foundation of healthcare systems for centuries (Libster, 2004), yet many people may feel disconnected from their environment and the plants that are responsible for their food, shelter, and medicine. They may have no knowledge of what it takes to grow the tomato and prepare the tomato sauce that is on their pizza, or what plant has been the prototype for the newest cancer drug. Then, lacking this knowledge, they are faced with the decision points that have always come with use of medicinal plants. Marijuana is a plant no different from any other. It has many uses and forms, as well as hundreds of constituents, all seemingly at odds when the plant is examined in its reduced parts – but with scientific evidence of an intricate and powerful synergy of substances, an "entourage of effects," when examined as a whole (Russo, 2011). Herbalists, who are often community experts on the subject of the application of medicinal plants, are an excellent referral resource for healthcare professionals who are learning to counsel people considering or already taking plant medicines such as marijuana (Libster, 1999). Nurses, pharmacists, and behavioral health practitioners can forge partnerships with knowledgeable herbalists to begin to address existing and emerging public health considerations and concerns.

Table 5-1: Marijuana-Focused Assessment Questions

- Are we talking about the same plant or plant constituent? Evidence for safe and effective use differs for whole-plant parts such as leaf or seed versus constituents such as delta-9-tetrahydrocannabinol (THC).
- What is the person's interest in marijuana? What does the person know about the traditional and biomedical evidence for the plant or plant constituent?
- What is the person's story for deciding to use marijuana? The way a person makes health decisions is helpful in planning care.
- How long is the person planning to take marijuana? Will the use be occasional or continual?
- Is there traditional or historical evidence for the way the person is planning to take marijuana?
- In what form is the person planning to take marijuana? Education, information, and advice are tailored to the form of use. The benefits and risks of smoking whole leaf are different from the benefits and risks of taking dronabinol.
- What questions does the person have about marijuana? For example, is he or she looking for a report from clinical research, professional advice based on clinical experience, therapeutic support, or a combination?
- What are the person's perceptions of the outcome of partnering with marijuana?

Note. From Western Schools, 2018. Adapted from Libster, M. (2012). The nurse-herbalist: Integrative insights for holistic practice. Neenah, WI: Golden Apple Publications.

Smoking tobacco products has been linked to health hazards related to the heat of combustion and the knowledge that long-term use can lead to chronic bronchitis and other diseases. Users of marijuana and healthcare professionals hold similar concerns about marijuana smoking. Table 5-1 suggests questions that healthcare professionals can ask people who are considering medicinal marijuana. The herb can be rolled into a cigarette for smoking, called a "joint," or smoked using a water pipe or "bong." In a bong, the smoke from the burning marijuana bubbles through the bong water, where it is cooled. It is important to note that particulate matter from the burning action is not removed by the water. Hashish is typically smoked using a pipe or bong, or mixed with marijuana and smoked as a joint or vaporized.

As electronic cigarettes (e-cigarettes) are becoming more popular with tobacco smokers, "vaping" with e-cigarettes and electronic vaporizers is emerging as a possible method for inhaling marijuana (Tashkin, 2015). People who use e-cigarettes believe that vaping is healthier, as well as more discreet because it produces less odor than smoking. Disadvantages are that vaping produces dry mouth and fewer positive marijuana effects (Etter, 2015). Marijuana buds and oil are often the product of choice for these devices rather than hashish, wax, or butane honey oil. In an exploratory study (Etter, 2015), 45% of individuals who smoked and vaped marijuana reported that vaping reduced their marijuana use, 37% said it had no impact on their marijuana use, and 6% said that it increased their marijuana use. Vaping is also less expensive than traditional smoking. One in vitro study concluded that "temperature-controlled, electrically-driven vaporizers efficiently decarboxylate inactive acidic cannabinoids and reliably release their corresponding neutral, active cannabinoids. Thus, they offer a promising application mode for the safe and efficient administration of medicinal cannabis" (Lanz, Mattson, Soydaner, & Brenneisen, 2016).

One literature review revealed something about marijuana that is somewhat counterintuitive: It suggests that marijuana increases rather than reduces forced vital capacity (FVC) in patients (Ribeiro & Ind, 2016). This effect may be related to the anti-inflammatory effects of the plant. However, the review also cited several community-based studies, all but one of which showed significant increase in symptoms of chronic bronchitis and use of acute care services for respiratory illness in people who frequently smoke marijuana.

An analysis of survey questions and standardized spirometry data from a cross-sectional study of adults in the United States who participated in the National Health and Nutrition Examination Survey from 2007 to 2010 showed that 59.1% had used marijuana and 12.2% had used marijuana in the last month. The effect of smoking marijuana was measured as the ratio or relationship between lung function scores recorded as forced expiratory volume and FVC. The study concluded that, despite marijuana smoke being a known irritant to the airways of the lungs, cumulative lifetime marijuana use, up to 20 joint-years, is not associated with adverse changes in the above spirometric measures of lung health. However, people who smoke marijuana for more than 20 joint-years may have a significant increased risk of lung disease when compared with those who have never smoked marijuana (Kemper, Honig, & Martin, 2015).

Smoking marijuana with tobacco

Tobacco (*Nicotiana tabacum*) is a sacred plant to First Nation people. It is used in plant medicine harvest and traditional ceremonies, and its smoke is thought to provide direct communication with the Creator through prayer (Personal communication, Cecilia Mitchell, Mohawk Elder, 2005). A successful harvest was thought to depend upon this communication with the Creator. Some believe that when European-American people took tobacco from the First Nation people and consumed it without making an offering to the Creator, the imbalance led to addiction, lung cancer, and other diseases. Tobacco was first linked to lung cancer in 1946 (Lee, 2012), yet it was never criminalized as was marijuana. Given the evidence, some people suggest that marijuana has been singled out for criminalization (Lee, 2012; McKenna, 1992). This analysis draws upon compelling historical evidence that is beyond the scope of this course, but such arguments are now being heard in many states as they begin marijuana decriminalization movements. The status of a plant or its products has no bearing on the facts of its physiological effects. In 1964, as "marijuana" was becoming a household word, the U.S. Surgeon General released public information about the health hazards related to cigarette smoking (Centers for Disease Control and Prevention [CDC], 2017). Tobacco growers still received government subsidies, while marijuana remained illegal. Martin Lee (*Smoke Signals*), Terence McKenna (*Food of the Gods*), and other botanical scholars feel that such seeming hypocrisy has fueled the public movement supporting the legalization of marijuana. However, when healthcare professionals counsel people while using evidence to weigh the risks and benefits of substances, it becomes a challenge to put marijuana side by side with tobacco, alcohol, and opiates. Marijuana differs from those other substances in being a hallucinogen.

Many people who smoke tobacco also smoke marijuana. A joint (marijuana cigarette) prepared with tobacco is known as a "spliff" or "kiff." A systematic review of 28 studies showed that marijuana users who also smoked tobacco were more dependent on marijuana, had more psychosocial problems, and had poorer cessation outcomes than those who used marijuana but not tobacco (Peters, Budney, & Carroll, 2012).

A large study involving 64,855 male participants, ages 15 to 49, found that marijuana use was not associated with tobacco-related cancers (Sidney, Quesenberry, Friedman & Tekawa, 1997). Another study of 138 tobacco smokers surveyed concerning marijuana use found that anxiety sensitivity was related to marijuana use. In other words, users of marijuana seemed to experience anxiety more easily than they might when not using marijuana. The 25-item and 5-subscale Marijuana Motives Measure and the Anxiety Sensitivity Index-3 were the instruments employed in the study (Norberg, Olivier, Schmidt, & Zvolensky, 2014). Healthcare professionals may want to consider helping clients who are low in anxiety sensitivity and who use both marijuana and tobacco to focus on choosing alternative recreational behaviors that are associated with less health risk than smoking marijuana.

A preliminary study to evaluate the feasibility (i.e., intervention, utilization, safety, and acceptability) of group smoking-cessation programs and changes in substance use behavior found that these programs showed promise for individuals who smoked both tobacco and marijuana. The study was conducted with 77 adults who used marijuana at least once a week and tobacco cigarettes daily. The subjects participated in five or six group sessions that utilized motivational interviewing, cognitive-behavioral therapy, and self-control training. The treatment completion rate was 62.3% after 9 months. Abstinence rates for tobacco cigarettes and marijuana were 32.5% and 23.4%, respectively (Becker, Haug, Kraemer, & Schaub, 2015).

CULINARY USE

Marijuana edibles, sometimes referred to as "medibles," are a popular form of the drug for people seeking lower doses of marijuana. For example, a person can make candy or brownies that contain a known amount, such as 10 mg, of herb. The person can then titrate the dose by eating one bite. Marijuana extracts and hashish oil are frequently prepared as edibles in the form of candy, gummies, chewing gum, and brownies and other pastries. The edibles market is growing rapidly in states that have legalized marijuana, as first-time users become attracted to the culinary version of medicinal marijuana (Montgomery, 2017). Repeated ingestion ("stacking") of edibles before delta-9-tetrahydrocannabinol (THC)-mediated hallucinogenic onset is common. In addition to dose-related hallucinogenic effects, naïve users frequently develop severe nausea and vomiting. The state of Colorado has passed a law making it illegal to market marijuana gummy candies shaped like animals, people, or fruit, to protect children, who cannot be expected to distinguish ordinary gummy candies from those prepared with marijuana (Matthews, 2017).

Manufacturers offer website and packaging instructions for their colorful and enticing confections, such as the following:

- Start small (5-10 mg) – Metabolism and body fat vary so absorption time varies.
- No mindless snacking – Take a "dose" and wait.
- Full effect may take 2 or 3 hours, so start slowly.
- Food in the stomach can affect absorption time.
- Alcohol will increase THC blood concentration.
- "Overdose" of an edible is signaled when a person vomits or is too "spacey" (for his or her liking).

The benefit of marijuana edibles is that they provide the person who uses marijuana, particularly the first-time user of marijuana, with a familiar and seemingly more controlled method of dose titration. A person can take one bite of a 10-mg hashish cookie and wait for the effect. A drawback of this method is its assumption that people will be patient. However, Americans have grown used to over-the-counter medications that boast immediate relief. The longer activation time of "medibles" has led to overingestion. In addition, the risk to children or any adult from enticing confectionaries fortified with marijuana is great.

Another public health concern is unexpected severe intoxications brought on by edibles with high cannabinoid concentrations. Despite efforts to standardize unit dosing (10 mg/unit in Colorado), a single brownie could contain the equivalent of 6 to 10 unit doses (Douglas et al., 2015). During the first 8 months after legalization in Colorado, the Rocky Mountain Poison Center reported 64 calls related to edible marijuana products. Most of the calls were from adults aged 20 years and older (40 of 64). Of these callers, 11 had gastrointestinal symptoms, including nausea and vomiting leading in some cases to dehydration. Of the edible exposures reported, 15% (6 of 64) were in children aged 5 years or younger (Douglas et al., 2015).

CHILD AND ADOLESCENT MARIJUANA USE

The two major issues related to marijuana use currently acknowledged as impacting the health of children and youth are exposure through edibles and the risk of early marijuana use on the development of the brain of a young person. Societies and organizations of health professionals need to avoid the missed opportunities that came with the tobacco industry's campaign to delegitimize scientific evidence of harm related to tobacco smoking as corporations continued to market to vulnerable youth. Risk of accidental exposure is especially worrisome. In addition to promoting scientific agendas, professional societies are being called upon to advocate for preserving indoor air quality, free from marijuana smoke, and to promote "child-resistant packaging, clear and truthful constituent labeling, and prominently displayed guidance on how to respond to potential emergencies" (Douglas et al., 2015, p. 1707).

Some disagree, believing that the concerns about marijuana in relation to children and youth may be unfounded and inflated. Animal studies sponsored by the National Institute on Drug Abuse involving megadoses of THC and a potent synthetic cannabinoid receptor type 1 agonist concluded that the young human brain was susceptible to the damage of marijuana. Martin Lee (2012) remarked, however, that the study had nothing to do with likely marijuana-use behavior of adolescents and merely stoked alarmism concerning marijuana's effects on young people's brains.

Studies have, however, demonstrated adverse effects of marijuana on adolescent health. Dougherty and colleagues (2013) found that, of all the cognitive and behavioral domains tested in adolescents aged 14 to 17 years (n = 45), it was impairments in short-term recall and impulse control that were associated with marijuana use after controlling for performances across all measures (Dougherty et al., 2013). Marijuana is also associated with increased risk for psychosis and functional impairment in adolescents (Bagot, Milin, & Kaminer, 2015).

By the time they graduate from high school, about 45% of U.S. teens will have tried marijuana at least once in their lifetimes (Johnston, O'Malley, Miech, Bachman, & Schulenberg, 2016). In 2015, nearly 22% of high school seniors reported current marijuana use, and 6% used marijuana daily. The annual Monitoring the Future survey has been tracking teen attitudes and drug use since 1975. Currently, the number of teens who think marijuana use is harmful is declining. This trend is concerning because there is growing scientific evidence that heavy, regular use of marijuana that begins during the teen years may lower a person's intelligence quotient and interfere with other aspects of functioning and well-being. The good news is that marijuana use did not increase significantly among youth from 2010 to 2015 (Johnston et al., 2016).

Available evidence does not strongly support or exclude a causal relationship between marijuana use by adolescents and psychosocial harm. However, marijuana use has been shown to be associated with psychological health problems, use of other illegal drugs, reduced educational attainment, and antisocial behavior (Macleod et al., 2004). Macleod and colleagues (2004) conducted a review of more than 200 publications reporting the findings of 48 longitudinal observational studies about the relationship between drug use by adolescents and psychological or social outcomes. The studies could not reach conclusions about the effects of specific drugs, but most of the reported drug-specific concerns were related to the use of marijuana.

Suicide risk

Wong, Zhou, Goebert, and Hishinuma (2013) analyzed data from the CDC's 2001 to 2009 Youth Risk Behavior Survey, with a sample of 73,183 high school students. They found that substance abuse was a strong risk factor for suicidal thoughts and behaviors among American high school students, with the strength of this relationship dramatically increasing with particular illicit drugs and a higher number of substances. Marijuana had similar risk to alcohol, but significantly less risk when compared with heroin, methamphetamines, cocaine, ecstasy, and inhalants. Swahn and colleagues also examined data in the Youth Risk Behavior Survey for their study published in 2012, which found an association between early marijuana use and suicidal ideation and suicide attempts for boys and girls in France and for girls only in the United States.

MATERNAL MARIJUANA USE

The 2017 American College of Obstetricians and Gynecologists Committee Opinion on marijuana use during pregnancy and lactation favors the discontinuation of marijuana for medicinal purposes. Currently, however, insufficient data exist for the evaluation of the effect of marijuana use during lactation. In 2017, Nora Volkow of the National Institute on Drug Abuse and Wilson Compton and Eric Wargo of the National Institutes of Health published a "Viewpoint" article in the *Journal of the American Medical Association,* citing the lack of data and potential risk to the fetus of marijuana use. The opinion reports that 34% to 60% of women who use marijuana continue using the drug during pregnancy and lactation. The report included a discussion of a meta-analysis that evaluated newborn birth weights and other parameters after in utero exposure to marijuana. Women who used marijuana less than weekly were not at increased risk of giving birth to a newborn of less than 2,500 g, and most reports have not shown a statistical association between marijuana use and preterm birth. Tobacco smoking, however, may increase the risk of preterm birth in marijuana users. A study conducted by De Genna, Goldschmidt, and Cornelius (2015, p. 626) found that "chronic maternal marijuana use across a decade was also associated with early sex in offspring (oral or vaginal sex by age 14). Early sexual behavior places these children at significantly higher risk of teenage pregnancy and HIV risk behaviors."

ETHICS, PATIENT ADVOCACY, AND FREE SPEECH

Each healthcare professional has his or her own personal view about medicinal marijuana use. Each profession has a code of ethics whose purpose is to guide professional practice and decision making. No legal or professional mandate exists requiring nurses to follow the American Nurses Association (ANA) *Code of Ethics for Nurses with Interpretive Statements.* Membership in the ANA and adherence to the *Code of Ethics* are voluntary. Two of the ethical provisions in the *Code* state that "the nurse's primary commitment is to the patient" and that the nurse "promotes, advocates for, and strives to protect the health, safety, and rights of the patient" (ANA, 2015, p. v). Behavioral health professionals and pharmacists have their own codes of ethics, though the commitment to patient/client health, safety, and rights is essentially the same as that found in the *Code of Ethics for Nurses.* A type of ethical dilemma occurs when healthcare professionals' beliefs, personal or professional, conflict with their commitment to providing care that is congruent with their professional ethic. This type of dilemma will be explored in this chapter's Case Study.

The U.S. Drug Enforcement Administration (DEA) continues to deny petitions to reschedule marijuana (DEA, 2016), citing a lack of scientific or medical evidence to support the change, along with a "high potential for abuse." The Department of Veterans Affairs has corroborated the DEA position by prohibiting the use of medicinal marijuana in its facilities. The Department of Justice has declared that the selling, cultivation, or distribution of marijuana is against federal law and that individuals engaging in these activities are subject to enforcement action. Yet millions of Americans are using marijuana. In 2002, in a case called *Conant v. Walters* (formerly called *Conant v. McCaffrey*), the U.S. District Court held that the First Amendment, which protects free speech, allows physicians to discuss and perhaps recommend medical marijuana use without punishment. In 2003, the U.S. Supreme Court upheld this decision (American Civil Liberties Union, 2003).

Case study 5-1: Interprofessional ethical dilemma in palliative care

A nurse, pharmacist, and social worker are involved in the care of Mrs. Smith, a 70-year-old female who is considering marijuana for the pain and anorexia she is experiencing with her cancer. Biomedical treatment has ended, and her physicians have told her that she is dying and is being moved to the palliative care service.

The healthcare professionals and Mrs. Smith live in a country (the United States) where marijuana is illegal and in a state where it is also illegal. But the conflict is that Mrs. Smith has a belief that marijuana might be the best solution to easing her suffering. Mrs. Smith reports no relief from medications, particularly for the anorexia. She has decided to start eating or smoking marijuana and asks her trusted team of healthcare professionals what type of marijuana she should buy and how much to use. Mrs. Smith states that she knows that marijuana is still illegal.

Questions

1. What are the issues that the team faces in processing the dilemma with Mrs. Smith?
2. What are Mrs. Smith's options regarding marijuana or alternative treatments?
3. Reverse roles with Mrs. Smith. What might you feel about the process of getting medicinal marijuana if you have decided it is best for you?

Answers

1. An ethical dilemma occurs when there seems to be no strong right or wrong answer to a situation, or when there may be more than one right answer. In this case, Mrs. Smith's healthcare professionals have a fiduciary responsibility to provide her with the best care and comfort. They have a responsibility to evidence-based practice, and there is clinical research and traditional evidence from hundreds of years of use in anorexia for using marijuana. Mrs. Smith is dying, causing her primary nurse and perhaps other members of the team, to struggle with a law prohibiting the use of marijuana to protect public safety. However, Mrs. Smith is actively dying and does not need the protection of the marijuana law.
2. By law, Mrs. Smith may not use marijuana. She is already fully informed about this legal situation and yet asks the team to help her anyway. The team can focus on the therapeutic value of their relationship with Mrs. Smith and use that relationship as a foundation for finding solutions to her anorexia and pain.
3. The controversy over medicinal marijuana can lead to feelings of confusion and anxiety. Reflective practice can lead to innovative solutions and decreased anxiety. Consider taking some time after this course to retreat for purposes of reflection on your own feelings and thoughts about marijuana. It is an unusual topic for many health professionals, who are used to dealing with drugs rather than with whole-plant remedies. Reflect on any changes in your thinking and feelings about marijuana that may have occurred as a result of taking this course and how such changes might alter your approach to the care of individuals using marijuana or considering its use. Many practitioners and members of the public favor retaining prohibition, while others favor legalization. Whatever your thoughts and feelings on the subject of medicinal marijuana might be, reflect on what you, as a healthcare professional, will add to shared decision making and to civil discourse.

COURSE SUMMARY

Many healthcare professionals, who are called upon every day to make life-transforming, if not life-saving, decisions with people experiencing distress, discomfort, and disease, remain subject to the confusion and politicization surrounding medicinal marijuana use. It is *the* plant of this time in history that is a catalyst for change. All medicinal plants are catalysts for change in body, mind, and spirit. Yet the impact of their catalyzing action is a matter of degree and location. Marijuana, like all medicinal plants throughout history, continues to "share" its benefits and its risks with humans. Healthcare professionals in nursing, pharmacy, and behavioral health are at the leading edge of plant, drug, and therapy discovery. People in many states are demanding access, and healthcare professionals' approach to evidence-based practice must respond to the implications of that demand. It may not be good enough to wait years for randomized clinical trials of marijuana use to be conducted before engaging with the plant, its cannabinoids and terpenes, and the people who are already engaged in an experimental trial of their own making. Although a demand will always exist for clinical trials that seek to answer questions of causation, many people are relying on different ways of knowing and different evidence that also has been a foundational part of the history of science, medicine, therapy, and caring. The history and traditional evidence of use, and in the case of marijuana of abuse, are also important guides.

Case studies with one participant (n = 1) or large population studies with thousands of participants, as well as clinical trials and laboratory studies suggesting the plant's mechanism of action, all serve as useful evidence that informs vigilant healthcare professionals who are seeking a greater understanding of marijuana's role in human health and healing. The body of clinical scientific evidence for safe and efficacious use is also informed by knowledge and understanding gleaned from the health beliefs, language, and self-care practices of people engaging in what some say is an emerging culture, an evolution, or a change in consciousness. From the perspective of history, marijuana, like other plants in times past, has become the next expression of people's hopes for healing and peace that can come from entering new domains of scientific exploration. Marijuana at the very least has already inspired much scientific musing at the crossroads where phytocannabinoids meet endocannabinoids.

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Final Examination Questions

Select the best answer for each question and then proceed to **EliteLearning.com/Book** to complete your final examination.

21. Recreational use of marijuana is best defined as the user's intention to:
    a. Become intoxicated.
    b. Relieve pain.
    c. Sleep.
    d. Exercise.
22. The resin or sap that forms on marijuana and is collected for use is known as:
    a. Dope.
    b. Joint.
    c. Hashish.
    d. Smack.
23. The main psychoactive constituent in marijuana is:
    a. Cannabidiol.
    b. *Cannabis indica.*
    c. Lysergic acid diethylamide (LSD).
    d. Delta-9-tetrahydrocannabinol (THC).
24. The paradoxical stimulating and sedating effect produced by smoking marijuana is similar to the effect produced by:
    a. Alcohol.
    b. LSD.
    c. Antidepressants.
    d. Coffee.
25. Hemp is a strain of *Cannabis:*
    a. Indica that is high in THC.
    b. Sativa that is low in THC.
    c. Indica with no THC.
    d. Sativa that is high in THC.
26. In the 1800s, marijuana was used by physicians in the treatment of:
    a. Migraine headaches.
    b. Cancer.
    c. Osteoporosis.
    d. Tetanus.
27. The effects of eating hashish are not felt for at least:
    a. 5 to 10 minutes.
    b. 15 to 20 minutes.
    c. 30 to 60 minutes.
    d. 70 to 90 minutes.
28. Common effects of smoking *Cannabis sativa* include:
    a. Whole-body relaxation.
    b. Sleepiness.
    c. Calmness.
    d. Optimism.
29. A major risk factor for marijuana use disorder is:
    a. Use before age 18.
    b. Eating hashish.
    c. Adulteration.
    d. Use of *Cannabis indica.*
30. Marijuana withdrawal symptoms can be similar to:
    a. Cocaine withdrawal.
    b. LSD withdrawal.
    c. Nicotine withdrawal.
    d. Alcohol withdrawal.
31. Two major phytocannabinoids responsible for medicinal effects of marijuana are delta-9-tetrahydrocannabinol (THC) and:
    a. Cannabidiol.
    b. 3-hydroxycannabidiol.
    c. Cannabis.
    d. Endocannabioid.
32. The two drugs the U.S. food and Drug Administration has approved for use in chemotherapy-induced nausea and vomiting are dronabinol and:
    a. Nabitan.
    b. Nabilone.
    c. Nabumetone.
    d. Nabazenil.
33. Cannabinoid type 1 (CB1) receptors are found mainly in the:
    a. Immune system.
    b. Gut.
    c. Brain.
    d. Lungs.
34. Anandamide and 2-AG are examples of:
    a. Hormones.
    b. Phytocannabinoids.
    c. Glutamate.
    d. Endocannabinoids.
35. The reason for marijuana's effect on the human brain is thought to be that:
    a. Delta-9-tetrahydrocannabinol (THC) is similar to endocannabinoids.
    b. Cannabinoid type 1 (CB1) is similar to endocannabinoids.
    c. Cannabidiol (CBD) is similar to endocannabinoids.
    d. Gamma-aminobutyric acid (GABA) is similar to endocannabinoids.
36. A new physiological theory about endocannabinoid system (ECS) deficiency has been supported by some evidence from studies of people with:
    a. Bipolar disorder.
    b. Allergies.
    c. Chronic obstructive pulmonary disorder.
    d. Posttraumatic stress disorder.
37. According to a 1999 Institute of Medicine report, the major adverse effect of oral THC in older adults with no previous experience with taking marijuana is:
    a. Stroke.
    b. Nausea.
    c. Disorientation.
    d. Depression.
38. The gateway theory, when applied to marijuana use, is unsupported mostly due to:
    a. Confounding effects of the environment.
    b. Evidence for previous drug use.
    c. Increased public acceptance of marijuana.
    d. Lack of clear evidence for causation.
39. Clinical research on use of marijuana as a whole herb faces the challenge of:
    a. Enrolling participants.
    b. Standardizing plant constituents.
    c. Eliminating adulterants.
    d. Finding plants free of delta-9-tetrahydrocannabinol (THC).
40. Research on epilepsy has shown promising evidence for the use of:
    a. Cannabidiol (CDB).
    b. THC.
    c. Hemp oil.
    d. Synthetic cannabinoid (WIN55212-2).

41. Research has shown solitary marijuana use to be particularly associated with which mental illness?
    a. Phobia disorder.
    b. Obsessive-compulsive disorder.
    c. Social anxiety disorder.
    d. Panic disorder.
42. A marijuana study by Schoeler and colleagues (2016) found that relapse of psychosis may be related to:
    a. Eating after smoking marijuana.
    b. Changing the frequency of marijuana use.
    c. Drinking alcohol.
    d. Stopping therapy.
43. Self-titration of marijuana for cancer pain management is considered by at least one expert (Abrams, 2016) to be:
    a. An uncommon practice.
    b. Marginally effective.
    c. The safest option.
    d. The best-known use of nabilone.
44. The major difference between federal and state marijuana law is that:
    a. Federal law prohibits marijuana use for all purposes and by anyone.
    b. State laws prohibit marijuana use for all purposes and by anyone.
    c. Federal law allows marijuana use for medical purposes only.
    d. State laws allow marijuana use for palliative care only.
45. A resource that can be used for monitoring a state's legalization status for medicinal marijuana is the:
    a. National Conference of State Legislatures.
    b. Federal Bureau of Narcotics.
    c. U.S. Food and Drug Administration.
    d. U.S. Drug Enforcement Administration.
46. Supportive psychotherapy has been shown to be effective in outpatient treatment of marijuana dependence in combination with:
    a. Antipsychotic medication.
    b. Mindfulness-based training techniques.
    c. Nutrition counseling.
    d. Family therapy.
47. A systematic review of the literature shows that marijuana users who smoke tobacco are:
    a. Less dependent on marijuana.
    b. More dependent on marijuana.
    c. Equally dependent on marijuana and tobacco.
    d. Not dependent on marijuana.
48. The growing concern about "medibles" is their:
    a. Accessibility to children.
    b. Sugar content.
    c. Interaction between marijuana and chocolate.
    d. High number of calories.
49. According to one study, the risk of suicide in adolescents who use marijuana is the same as for those who use:
    a. Alcohol.
    b. Amphetamines.
    c. Heroin.
    d. Cocaine.
50. An ethical dilemma related to medicinal marijuana use is thinking that it should be:
    a. Illegal.
    b. Illegal and refusing to care for a user.
    c. Legal.
    d. Legal and being prohibited by law from suggesting it for pain management.

Chapter 4: New Clinical Guidelines for the Management of Hypertension

3 Contact Hours

By: Katie Blair, PharmD, Rph

Author Disclosure: Katie Blair and Colibri Healthcare, LLC do not have any actual or potential conflicts of interest in relation to this lesson.

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Learning objectives

Upon completion of this course the learner should be able to:

- Characterize the different stages of high blood pressure including elevated blood pressure, Stage 1 hypertension, Stage 2 hypertension, and hypertensive crisis.
- Distinguish between primary (also known as essential) and secondary hypertension.
- Describe two myths associated with the symptoms of hypertension.
- Name three factors implicated in the development of hypertension.
- Identify three components of the DASH diet.
- Name one antihypertensive agent identified by JNC 8 for initial treatment of black hypertensive patients.
- List three class side effects associated with the use of beta blockers.
- Identify one advantage of combination drug product use to treat hypertension.
- Describe one potentially neurologic abnormality that is associated with a hypertensive emergency.

Introduction

Blood pressure can be thought of as a quantitation of the force of blood resulting from the beating heart, relative to the resistance offered by the vascular system. The measurement of blood pressure is generally assessed with two distinct measurements, expressed as millimeters of mercury (mmHg):

- Systolic blood pressure: Peak pressure associated with the heart's contractions.
- Diastolic blood pressure: A resting pressure measured between heartbeats.

For most healthy adult patients, normal blood pressure is defined as a systolic blood pressure that is less than 120 mmHg and a diastolic blood pressure that is less than 80 mmHg (120/80 mmHg). Pressures fluctuate throughout the day and are dependent on a patient's level of activity. If a patient is excited, nervous, or exerting him/herself, blood pressure will typically rise. It will then fall back to normal when the activity concludes. Blood pressure is also a function of age and body size. For example, compared to older teenage children or adults, newborn babies have lower blood pressures. Hypertension is a common pathologic condition that describes higher-than-normal blood pressure (NHLBI, 2017).

Abnormal blood pressure - Hypertension may be diagnosed based on an increased systolic blood pressure, an increased diastolic blood pressure, or increases of both. Hypertension can be categorized by the extent of increases in blood pressure into distinct stages, as described in the following table (ACC, 2017):

Table 1: Stages of Systolic/Diastolic Pressure

Stage	Systolic pressure (mmHg)	Diastolic pressure (mmHg)
Elevated blood pressure.	120 – 129.	< 80.
Stage 1 hypertension.	130 – 139.	80 – 89.
Stage 2 hypertension.	≥ 140.	≥ 90.
Hypertensive crisis*.	> 180.	> 120.

**The requirements of a diagnosis of Hypertensive Crisis can be met by systolic and/or diastolic elevations, e.g., systolic blood pressure of 190 mmHg and diastolic blood pressure of either 110 or 130 mmHg would qualify.*

It is critical to note that these stages of blood pressure are based on November 2017 guidelines that were issued by the American College of Cardiology (ACC) and the American Heart Association (AHA). These new definitions are at lower levels than those previously employed and remove the old designation of prehypertension. These new levels are designed to identify a larger number of people (estimated to include 46% of American adults) in an effort to facilitate earlier interventions. It is expected that this will have the greatest impact on younger patients: It will triple the prevalence of high blood pressure in men under the age of 45 and will double the incidence in women in that same age group. Typically, patients with elevated blood pressure (not Stage 1/2) should be encouraged to embrace healthy lifestyle changes and then be re-assessed in three to six months (ACC, 2017). Further, the ranges presented in the table above are

intended for use in adults who are not currently suffering from any comorbidities. For example, in patients with diabetes or chronic kidney disease, a normal blood pressure is defined as less than 130/80 mmHg (NHLBI, 2017).

Primary hypertension

There are two key varieties of hypertension: primary hypertension and secondary hypertension.Primary hypertension, also known as essential hypertension, refers to high blood pressure for which there is no obvious cause. Nonetheless, its definition also implies that treatment of elevated blood pressure will result in significant clinical benefit. Due to differences in each individual's cardiovascular risk, that benefit will vary from patient to patient (Oxford Medicine Online, 2015). A hypertension diagnosis can be made at such time that the average of two or more diastolic blood pressure assessments, on at least two subsequent patient encounters, is ≥ 89 mmHg, or when the average systolic blood pressure readings on two or more subsequent encounters is consistently ≥ 140 mmHg. In cases where consistent systolic blood pressure measurements are ≥ 139 mmHg, accompanied by diastolic blood pressures of < 89 mmHg, a diagnosis can be made of isolated systolic hypertension (Carretero & Oparil, 2000). Isolated diastolic hypertension (IDH), defined as patients with a diastolic blood pressure > 89 mmHg and a systolic blood pressure < 139 mmHg, is more common in younger patients. It is not generally reported as a separate diagnosis. It appears that IDH is becoming more prevalent in sedentary males with higher body mass indices who live in developing countries (Midha, Lalchandani, Nath, Kumari, & Pandey, 2012).

Secondary hypertension

Secondary hypertension occurs in cases where high blood pressure stems from another medical condition. A variety of pathologies may result in secondary hypertension, including conditions that impact the health of the kidneys, arteries, heart, or the endocrine system. In some cases, secondary hypertension can also occur as a result of pregnancy. While the causes of primary hypertension are unknown, treatments are generally focused only on treating the high blood pressure. However, treatment of secondary hypertension can be more complex. In addition to efforts to reduce the blood pressure, proper treatment of secondary hypertension also requires attention to the underlying condition to decrease the risk of developing serious complications (Mayo Clinic, 2017).

Symptoms

Hypertension has a unique pathology as it typically has no overt symptoms. As a result, hypertension is referred to as the "silent killer." A number of myths regarding hypertension symptoms are believed; for example, a patient may suppose that hypertension is always accompanied by physical signs such as nervousness, difficulty sleeping, flushing, or sweating. However, most cases of high blood pressure are not associated with overt symptoms. Patients who experience a hypertensive emergency may occasionally experience headaches or nosebleeds, but these symptoms are not indicative of hypertension. The only certain way to recognize hypertension is through a clinical diagnosis, largely based on blood pressure assessment (AHA, 2017).

Prevalence

According to a recent report from the Centers for Disease Control and Prevention (2016), hypertension is common in the United States and afflicts one out of every three adults, or 75 million Americans. Of those impacted, just over half appropriately manage their hypertension. Care for these patients is expensive: Total expenditures—including costs for health care services, missed work, and medications—equals about $46 billion each year. Over the course of a lifetime, the risk of developing hypertension is similar between men and women. Nonetheless, more men than women are affected in those under 45 years of age. In older people (≥ 65 years of age), women are more susceptible to hypertension. Race and ethnicity also appear to be predictors of hypertension. Higher rates are present in African Americans than in Caucasians and Hispanics. Hypertension appears to be closely linked to mortality: Every day, nearly 1,000 deaths in the United States include hypertension as a primary or related cause. This extensive mortality is a result of the increased the risk of heart attack and stroke in patients with hypertension (CDC, 2016). The CDC estimates that (CDC, 2016):

- About one in every five people with hypertension are not properly diagnosed.
- Seven out of every ten American adults use medication to treat hypertension.
- In 2009, more than 55 million health care visits were attributed to the treatment of hypertension.

Pathology

It is estimated that the vast majority of diagnosed hypertension is of the primary variety and is without a known cause (Carretero & Oparil, 2000). Although the etiology is evasive, it is acknowledged that a collection of intertwined physiological mechanisms governs normal blood pressure. As a result, it is reasonable to expect that a perversion of these influences could be involved in the pathogenesis of hypertension. It is also fair to expect that the roles of such influences may vary between patients. In attempts to solve this puzzle, a number of factors have been interrogated. These factors include insulin resistance, the nervous system, obesity, genetics, endothelial function, prenatal nutrition, salt intake, and even low birth weight (Beevers, Lip & O'Brien, 2001).

Irrespective of the exact cause that leads to hypertension, it is known that in order to maintain normal blood pressure, a proper balance must exist between cardiac output and the resistance that blood flow encounters in the body. In many cases, established hypertension can be linked to an increase in peripheral resistance, rather than an increase in cardiac output. It is critical to note that such resistance is generally not a function of blood flow through large arteries or even capillaries. Rather, the main driver of peripheral resistance is flow through smaller arterioles, whose diameter is controlled by their smooth muscle cells. A prevailing theory is that contraction of these muscular blood vessels is related to intracellular calcium concentrations. In cases where these smooth muscles are chronically contracted, structural change of the arterioles may emerge, including a thickening of the arteriole walls. Such changes could result in irreversible increases in peripheral resistance. It is also believed that in the case of very early hypertension, an increase in peripheral vascular resistance are not to blame; rather, the elevations observed in blood pressure are a result of increased cardiac output related to overactivity of the sympathetic nervous system. As the body constantly evolves to compensate, an increase in peripheral arterial resistance could result in an effort to protect the capillary beds from the increases in blood pressure (Beevers et al., 2001).

Although current knowledge does not allow a complete explanation for primary hypertension, a brief examination

of some potential factors that result in hypertension can be instructive. Possible factors contributing to hypertension include:

- Renin-angiotensin system: Also known as RAS, it plays a critical role in regulating fluid balance and blood pressure in the body. If blood volumes or sodium levels become low, or if potassium is elevated, the kidney releases an enzyme called renin. The renin converts angiotensinogen to form the hormone angiotensin I. An angiotensin-converting enzyme (ACE) then turns angiotensin I into angiotensin II. Angiotensin II causes blood vessels to constrict, leading to increases in blood pressure (UKRO, 2015).
- Autonomic nervous system: Physiological models have long implicated the role of the autonomic nervous system in the control of various cardiovascular functions as they control blood pressure (often in response to environmental stimuli). Both observations and investigations have shown that an abnormal activation of the sympathetic nervous system is related to dysfunctional cardiovascular control, including both the promotion and amplification of primary hypertension. Recent literature has implicated both adrenergic and vagal abnormalities (Mancia & Grassi, 2014).
- Endothelial dysfunction: The endothelium is a tissue formed as a single layer of cells that serve as a lining to a variety of organs and body cavities, including blood vessels (Google, 2017). The endothelium plays a large role in determining the tone and structure of the vascular system. A key chemical that is able to influence the endothelium is nitric oxide (NO), which serves as a potent vasodilator, among other functions. Dysfunction of the endothelium, due to NO deficiency, has been implicated in the development of hypertension (Taddei, Virdis, Ghiadoni, Sudano, & Salvetti, 2001).
- Vasoactive substances: A number of factors are known to have a pronounced impact on vascular tone, with nitric oxide playing the most dominant role. Additional vasoactive substances include cyclooxygenase and other endothelium-derived contracting factors (Lüscher, Yang, Diedrich, & Buhler, 1989).
- Insulin resistance: Insulin resistance can lead to elevated levels of insulin, which impact normal intracellular communication, to include blood pressure regulating signals. These changes can cause increased cardiac output, as well as arterial constriction. Further, increased insulin can create a sodium and potassium imbalance (increasing blood volume), as well as calcium and magnesium (leading to vasoconstriction). All of these events can then increase blood pressure (Whitaker, 2017).
- Genetic factors: Although hereditary predisposition to hypertension is well acknowledged, it is complex and, at times, difficult to understand. Many genes are involved, but no single gene has been implicated as a major factor contributing to hypertension. Alternatively, it is thought that a number of different genes conspire to influence blood pressure, with each possibly reacting to a variety of different environmental stimuli. Research has suggested that 30 to 50 percent of the variance in blood pressure across a population is attributable to genetic predisposition, and about half to other environmental influences (Butler, 2010).
- Intrauterine influences: Evidence suggests that improper nutrition of pregnant women can negatively impact the vascular health of a child later in life. It is thought that proper levels of energy and protein are key determinants for fetal programming. While a number of essential nutrients are needed, maternal over nutrition can also lead to negative consequences. Children of obese or diabetic mothers are more prone to hypertension (Szostak-Wegierek, 2014).

History of treatments for hypertension

The proper management of hypertension may possibly be one of the greatest medical success stories of the 20th century. Although the assessment of blood pressure dates back well into the 1800s, conclusive evidence documenting "normal" blood pressure and potential treatment developments did not occur until the last half of the 20th century. Prior to the early 1970s, hypertension was not routinely treated in contemporary medical practice. In fact, prior to 1970, hypertension was not treated except in cases where diastolic pressure exceeded 110 mmHg. For example, if a blood pressure assessment of 170/98 was obtained prior to 1970, it would be simply noted in the patient record, without intervention. Beginning in about 1970, the so-called "War on Hypertension" began. Routine blood pressure monitoring began, taking place at medical facilities, and at a variety of non-medical settings. It truly was a national effort and included television public service announcements. Even so, major questions persisted: What were target blood pressures and what medication could best manage hypertension? Medical professionals performed extensive research to answer these critical queries. Through research conducted in the 1970s and 1980s, a diastolic blood pressure target of less than 90 mmHg was established (Guthrie, 2012).

By the 1980s, medical professionals saw a noticeable decline in death caused by cardiac issues and stroke. Since the mass treatment of hypertension was the only major change in treatment paradigms, this improvement in mortality was generally attributed to new blood pressure management efforts.

In the 1990s, medicine entered into a new way of thinking. While earlier efforts focused on the remedy of elevated diastolic blood pressure, new research suggested the benefit of also treating patients with elevated systolic blood pressures—even if their diastolic pressures were within the normal range. Again, these new interventions resulted in a decrease in cardiac issues and stroke rates, especially in older patients. Nationwide health surveys have demonstrated that progress in hypertension management continues to improve, from target achievements of about 10 percent in 1970 (Guthrie, 2012), to just over 50 percent in the most recent surveys (CDC, 2016).

Non-pharmacologic treatment of hypertension

Treatment of hypertension is a critical component of health maintenance. Proper management of hypertension has been associated with decreases in the rates of stroke (with an average of 35 to 40 percent reduction), heart attack (a 20 to 25 percent reduction), and heart failure (with greater than a 50 percent reduction) (WebMD, 2017). As with many chronic pathologies, the prevention of hypertension is key. To this end, all patients should make appropriate lifestyle changes that include healthy eating, quitting smoking and ensuring an adequate level of physical exercise. In cases where hypertension is diagnosed, despite proper lifestyle changes, medication is typically indicated. Nonetheless, even if prescribed medication, patients must be encouraged to continue with healthy lifestyle choices (WebMD, 2017).

A number of critical lifestyle choices can help in the prevention and management of hypertension. Examples of positive lifestyle changes include, but are not limited to (WebMD, 2017):

- Weight loss in the case of overweight or obese patients.
- Becoming more active: People should get at least 30 minutes of aerobic exercise at least five times a week.
- Consumption of healthy foods, including more vegetables, fruits, and low-fat dairy products, coupled with reductions in saturated and total fats. This heart-healthy diet is known as the DASH diet (Dietary Approaches to Stop Hypertension) (WebMD, 2017). More information on the DASH diet is available here: http://dashdiet.org/default.asp
- Reducing sodium intake to less than 1,500 milligrams per day if hypertensive. or less than 2,300 milligrams per day for healthy adults.
- Limiting alcohol.

Exercise and diet

While pharmacological treatments for hypertension are well-established, they may not be the best approach for all patients due to their level of hypertension, cost, the incidence of adverse events and compliance issues. Moreover, some of the comorbidities associated with hypertension, such as insulin resistance and hyperlipidemia, can be exacerbated by certain anti-hypertensive medications. As a result, extensive research has been accomplished to determine the most useful behavioral interventions for the treatment of hypertension. The most critical modifications are exercise and diet. Exercise has the potential to lower systolic and diastolic blood pressure by about 3.5 and 2.0 mmHg, respectively. Patients who follow diets high in low-fat dairy products, fruits, and vegetables can expect reductions of 5.5 mmHg in systolic blood pressure, and 3.0 mmHg in diastolic blood pressure. Further, weight loss is a reliable tool to reduce blood pressure. On average, an 8-kg (approximately 18 pound) weight loss is associated with systolic and diastolic blood pressure reductions of 8.5 mmHg and 6.5 mmHg, respectively. These reductions appear to be cumulative, with decreases of 12.5 mmHg (systolic blood pressure) and 7.9 mmHg (diastolic blood pressure) in overweight hypertensive patients who embrace both weight loss and exercise. Moreover, there is clinical evidence that decreases in blood pressure that results from exercise and weight loss lead to decreases in left ventricular mass/wall thickness, decreased arterial stiffness, and improved endothelial function. Taken either alone or in combination, available data supports the benefit of positive behavioral modifications in treating hypertension (Bacon, Sherwood, Hinderliter, & Blumenthal, 2004).

In order to assess the impact of individuals' sodium intake on blood pressure, Sacks et al. (2001) conducted a study of 412 randomized participants. Participants were instructed to eat either an average American diet or a modified DASH diet. Within those cohorts, each participant ate foods with high, intermediate, and low levels of sodium for 30 consecutive days. In patients who received the control diet, sodium reductions from the high to the intermediate level resulted in systolic blood pressure reductions of 2.1 mmHg. The same reductions in subjects who followed the DASH diet experienced reductions of 1.3 mmHg. A further reduction, from intermediate to low levels of sodium, resulted in additional decreases of 4.6 mmHg in the control diet subjects and 1.7 mmHg in the DASH diet subjects. Similar results were observed irrespective of hypertensive diagnosis or ethnicity. In all cases, the DASH diet was associated with a significantly lower systolic blood pressure at each of the sodium intake levels. The most extreme difference was observed when comparing high sodium, control diet patients with hypertension to low sodium, DASH diet subjects (11.5 mmHg). Investigators concluded that both the DASH diet and sodium reduction were effective mechanisms to lower blood pressure—the greatest impacts were observed when sodium reduction was combined with the DASH diet. In order to deliver meaningful clinical benefit, a lifelong commitment to these dietary changes is required (Sacks et al., 2001).

Alcohol use

While heavy alcohol use has been known to increase the risk of hypertension, there was no known association between light-to-moderate use of alcohol and hypertension prior to a study by Sesso, Cook, Buring, Manson, & Gaziano (2008). In this examination, they followed a total of 28,848 women and 13,455 men for a median interval of 10.9 and 17 years, respectively. At their baseline, all subjects were free from diagnoses of hypertension, cardiovascular disease, and cancer. Over the course of the study, a total of 8,680 women and 6,012 men developed hypertension (defined in this study as either a systolic blood pressure ≥ 140 mmHg, or a diastolic blood pressure ≥ 90 mmHg). When adjustments were made to account for differences in lifestyle, the relationship between consumption levels and the development of hypertension differed between the sexes. In women, benefits (reduction in instances of hypertension) realized with light to moderate alcohol intake (one to three drinks per day) were ablated by heavy alcohol usage. The risk of hypertension development seemed to parallel the total alcohol intake. Alternatively, the risks in men were significantly associated with alcohol intake at any level. In summary, while women can safely consume three drinks per day, even a single drink for men can increase the risk of hypertension (Sesso et al., 2008).

Lifestyle changes are powerful tools and are useful for both the prevention and the management of diagnosed hypertension. Pharmacy professionals, through comprehensive patient education efforts, are well-suited to help their patients understand and appreciate the need to make appropriate lifestyle decisions.

Pharmacologic treatment of hypertension

In the case where lifestyle modifications are not sufficient to manage hypertension, medications may be required. Examples of medication classes that are typically useful in the management of hypertension include, but are not limited to (WebMD, 2017):

- Angiotensin-converting enzyme (ACE) inhibitors.
- Angiotensin II receptor blockers (ARB).
- Diuretics.
- Beta blockers.
- Calcium channel blockers.
- Alpha blockers.
- Alpha agonists.
- Renin inhibitors.
- Combination medications.

In order to best guide the pharmacological management of hypertension, a number of professional panels have convened over the years to develop treatment paradigms that are best suited to individual patient situations. Out of a total of over 400 nominees with expertise in hypertension, 50 panel members were appointed to serve on the Eighth Joint National Committee (JNC 8) to develop evidence-based recommendations for the treatment of hypertension, especially geared toward the primary care clinician. The JNC is one of the foremost regulatory bodies tasked with providing guidance on the prevention, detection, evaluation, and treatment of hypertension (Ukpabi & Ewelike, 2017). The entire panel reviewed and discussed comments on the JNC's recommendations between March and June 2013 and incorporated them into a final revised document (James et al., 2014).

Highlights from the JNC 8 provide guidelines for the rational treatment of hypertension. In a general population of adults at least 60 years old, drug therapy should commence in cases where systolic pressure exceeds 150 mmHg, or if a diastolic blood pressure is 90 mmHg or greater (AAFP, 2014). It is critical to note that recommendations from JNC 8 were not received without controversy. One key area of dissent revolved around the first recommendation, which increased the systolic blood pressure threshold for patients older than 60 years. Members of both the review committee and the practice community believed that this position was not well supported by the available data and could lead to suboptimal treatment scenarios in patients at risk for cardiovascular events. Possibly as a result of these points of discord, the ACC and the AHA developed their new, more stringent guidelines (Hernandez-Vila, 2015).

According to the ACC/AHA guidelines, the initiation of medications designed to lower blood pressure is encouraged in patients with an average systolic blood pressure of 130 mmHg or higher, or an average diastolic blood pressure of 80 mmHg or higher (Whelton et al., 2017).

At the time of this writing, these new guidelines did not appear to be consistently adopted. Although a transition to these new practice guidelines may take some time, clinicians should consider these new approaches as applicable to their patients. This program will rely on recommendations from both guidance documents, as appropriate (more conservative treatment thresholds from the ACC/AHA guidance; general treatment considerations from JNC 8).

The JNC 8 provides pharmacologic treatment guidelines. In general, in non-Black populations, initial interventions should employ some combination (either/or) of a diuretic, calcium channel blocker, ACE inhibitor, or ARB (either as monotherapy, or in combination, as appropriate). In Black populations, a typical first-line approach should include a diuretic and/or calcium channel blocker. After initiating treatment, blood pressure should be regularly monitored. If the target blood pressure is not obtained within the first month, the dosage of initial medication should be increased, or additional drugs should be considered. In no instance should an ARB be co-administered with an ACE inhibitor. During this time, critical lifestyle choices must be reinforced, and blood pressure should be monitored. In cases where target blood pressures cannot be obtained with the use of prescribed medications, antihypertensive drugs from other classes (such as ß-blockers) may be considered. Moreover, in some cases, a referral to a practitioner who specializes in the treatment of hypertension may be indicated. Lastly, it is likely beneficial to include either an ARB or ACE inhibitor in patients afflicted with CKD, since these medications have been shown to provide kidney outcome benefits (AAFP, 2014). The most current ACC treatment and follow-up guidelines are shown in Figure 1.

Figure 1. Hypertensive Treatment and Follow-up, as described in the 2017 ACC Treatment Guidelines

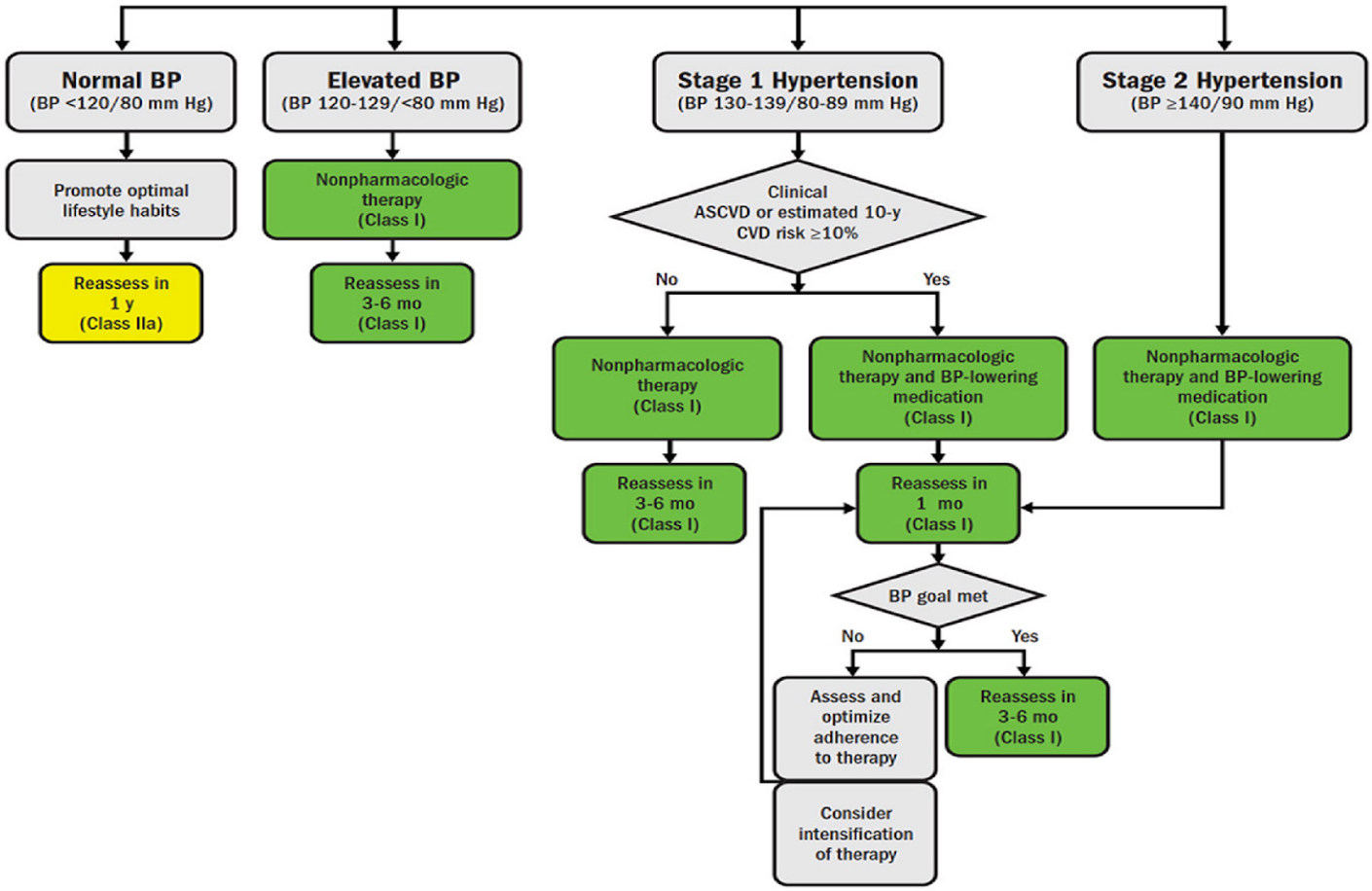

Figure 1 source: American College of Cardiology. (2017). The 2017 High Blood Pressure Guideline: Risk Reduction Through Better Management. Retrieved from http://www.acc.org/latest-in-cardiology/articles/2017/11/14/14/42/the-2017-high-blood-pressure-guideline-risk-reduction-through-better-management

Angiotensin-converting enzyme (ACE) inhibitors

Angiotensin-converting enzyme (ACE) inhibitors are useful in the treatment of a variety of maladies in addition to hypertension, including scleroderma and migraine headaches. The angiotensin-converting enzyme is responsible for the production of angiotensin II, a protein that narrows blood vessels and releases hormones that result in an induction of greater cardiac output. These modulations lead to an increase in blood pressure. Therefore, appropriate levels of ACE inhibition result in the relaxation of blood vessels coupled with a decrease in cardiac output. These changes ultimately result in blood pressure reduction (Mayo Clinic, 2017b).

The U.S. Food & Drug Administration has approved the use of a number of ACE inhibitors. Two critical points to keep in mind when considering the use of an ACE inhibitor for hypertension treatment are (Mayo Clinic, 2017b):
1) In general, these medications are less effective in older than younger patients.

2) ACE inhibitors generally are less efficacious in Black patients than White patients.

Examples of ACE inhibitors include:

- Benazepril (Lotensin: Novartis) – Benazepril is available in tablets of 5 mg, 10 mg, 20 mg, and 40 mg (Novartis, 2012).
- Captopril (Capoten: Par Pharmaceuticals) – Captopril is available in tablets of 12.5, 25, 50, and 100 mg (Par, 2012).
- Enalapril (Vasotec: Valeant Pharmaceuticals) – Enalapril is available in tablets of 2.5, 5, 10, and 20 mg (Valeant, 2011); as a solution for intravenous (IV) injection of 1.25 mg/mL; and as an oral solution of 1 mg/mL (Globalrph, 2017).
- Fosinopril (Monopril: Teva) – Fosinopril is available in tablets of 10, 20, and 40 mg (Teva, 2016).
- Lisinopril (Prinivil: Merck; Zestril: AstraZeneca) – Lisinopril is available as 5, 10, and 20 mg tablets (Merck, 2016); Zestril is available as 2.5, 5, 10, 20, and 40 mg tablets (AstraZeneca, 2008).
- Moexipril (Univasc: UCB) – Moexipril is available in tablets of 7.5 and 15 mg (UCB, 2016).
- Perindopril (Aceon: Patheon) – Perindopril is available in tablets of 2, 4, and 8 mg (Patheon, 2012).
- Quinapril (Accupril: Pfizer) – Quinapril is available in tablets of 5, 10, 20, and 40 mg (Pfizer, 2017).
- Ramipril (Altace: Pfizer) – Ramipril is available in capsules of 1.25, 2.5, 5, and 10 mg (Pfizer, 2017b).
- Trandolapril (Mavik: AbbieVie) – Trandolapril is available in tablets of 1, 2, and 4 mg (AbbieVie, 2017).

ACE inhibitor class effects

ACE inhibitor use is fairly widespread in the treatment of hypertension because of its relatively benign adverse event profile. Nonetheless, adverse events are always possible. Side effects associated with ACE inhibitors include dry cough, hyperkalemia, dizziness, headache, fatigue, and hypogeusia (a reduced ability to taste things such as sweet, sour, bitter, or salty substances). Although it is rare, angioedema has been observed in patients who take ACE inhibitors. If angioedema occurs in the throat, this adverse event can be life-threatening and requires immediate medical attention (Mayo Clinic, 2017b).

Due to an increased risk of teratogenicity (fetal renal damage), ACE inhibitors are contraindicated for use during the second and third trimesters of pregnancy. Although some data contradicts the use of ACE inhibitors during the first trimester, the data is controversial and is not conclusively linked to adverse fetal outcomes (Ray, Vermeulen, & Koren 2007).

ACE inhibitors are known to partition into breast milk. The appropriateness of nursing mothers who use these medications are dependent on the age of the infant and the specific agent. Due to the potential risk of profound neonatal hypotension, these drugs should be avoided by nursing mothers in the first few weeks of life. Pre-term infants are at a higher risk than are full-term babies. In the case of mothers who breastfeed older infants, data exists that supports the use of quinapril, captopril, and enalapril. Babies should be monitored for signs of hypotension (GPnotebook, 2017).

Although ACE inhibitors are not largely susceptible to pharmacokinetic drug-drug interactions, clinicians should be aware of a number of potential, clinically significant pharmacodynamic drug interactions that are associated with the use of these medications. For example, in patients who are sodium and/or volume-depleted from diuretic usage, excessive decreases in blood pressure— to the extent of symptomatic hypotension—are possible. If co-administered with potassium-sparing diuretics, hyperkalemia may occur, especially in cases of patients with renal insufficiency. When ACE inhibitors are combined with nonsteroidal anti-inflammatory drugs (NSAIDs), the potential for acute renal failure should be considered. Lastly, clinicians should be vigilant for occurrences of severe hypersensitivity in patients also receiving allopurinol (Mignat & Unger, 1995).

A number of studies to assess the use of ACE inhibitors in the management of hypertension and the prevention of morbidity and mortality have been performed to date. For example, the Captopril Prevention Project (CAPPP), described in a publication by Hansson et al. (1999), was designed to characterize the effect (endpoint: cardiovascular morbidity and mortality) of ACE inhibitors compared to conventional therapy (diuretic and beta blocker) in 10,985 hypertensive patients. Patients were evenly divided between the two groups. The mean follow-up time was 6.1 years. Primary endpoints occurred 11.1 times per 1,000 patient years in the captopril group, compared to 10.2 times per 1,000 patient years in the conventional treatment group. Cardiac mortality was less frequent in the captopril group (76 events) than in the conventional treatment group (95 events). Further, the rate of myocardial infarction was the same in both groups. Significant differences in the occurrences of stroke were observed: 189 strokes were observed in the captopril group; 148 were observed in the conventional treatment arm. Investigators concluded that there was no difference between captopril and conventional therapy in terms of efficacy in the prevention of cardiovascular morbidity and mortality. They hypothesized that the difference in the occurrence of stroke was likely due to lower blood pressures at baseline in patients randomized to conventional therapy (Hansson et al., 1999).

ANGIOTENSIN II RECEPTOR BLOCKERS (ARB)

Angiotensin is a protein present in humans that has a potential to impact the cardiovascular system in a variety of ways, including blood vessel constriction. Resultant increases in resistance can lead to hypertension. ARBs effectively block angiotensin II receptors, impeding the activity of angiotensin, facilitating blood vessel dilation, and decreasing blood pressure (Mayo Clinic, 2016).

The U.S. Food & Drug Administration (FDA) has approved a number of ARBs for the treatment of heart failure and hypertension. These include:

- Azilsartan (Edarbi: Takeda) – Azilsartan is available is available in tablets of 40 and 80 mg (Takeda, 2011).
- Candesartan (Atacand: AstraZeneca) – Candesartan is available in tablets of 4, 8, 16, and 32 mg (AstraZeneca, 2015).
- Eprosartan (Teveten: AbbieVie) – Eprosartan is available in tablets of 400 and 600 mg (AbbieVie, 2014).
- Irbesartan (Avapro: Bristol-Myers Squibb) – Irbesartan is available in tablets of 75, 150, and 300 mg (BMS, 2011).
- Losartan (Cozaar: Merck) – Losartan is available in tablets of 25, 50, and 100 mg (Merck, 2011).
- Olmesartan (Benicar: Daiichi Sankyo) – Olmesartan is available in tablets of 5, 20, and 40 mg (Daiichi Sankyo, 2011).
- Telmisartan (Micardis: Boehringer Ingelheim) – Telmisartan is available in tablets of 20, 40, and 80 mg (BI, 2011).
- Valsartan (Diovan: Novartis) – Valsartan is available in tablets of 40, 80, 160, and 320 mg (Novartis, 2006).

ARB class effects

Angiotensin receptor blockers are generally safe and well tolerated. Nonetheless, reported side effects include dizziness, angioedema, and hyperkalemia. More specifically, gastrointestinal adverse events (including diarrhea) have been observed in patients taking Benicar. In extreme cases of diarrhea, weight loss has also been observed.

Like ACE inhibitors, ARBs are known to cause fetal renal damage when administered in the second or third trimesters. Further, also like ACE inhibitors, the safe use of ARBs during the first trimester is controversial. Moretti et al. (2012) conducted a study of 138 women receiving ACE inhibitors or ARBs (a total of 28 patients were administered ARB) during the first trimester of pregnancy. Although there was no impact compared to a control group with regard to major malformations at birth, infants of mothers who received ACE inhibitors and ARBs exhibited lower birth weights at gestational age. Moreover, there was a significantly higher rate of miscarriage reported in these mothers. Investigators concluded that while these medications are not major human teratogens, they may be associated with an increased risk of miscarriage (Moretti et al., 2012). As a result, the use of ARBs in women who are pregnant, or who are planning to become pregnant, is not encouraged—except in cases where the clinical benefit outweighs the potential harm to the fetus (Moretti et al., 2012).

ARBs are known to be excreted into breast milk. The appropriateness of nursing mothers' use of these medications is dependent on the age of the infant and the specific agent. Due to the potential risk of profound neonatal hypotension, these drugs should be avoided by nursing mothers in the first few weeks of life. Pre-term infants are at higher risk than full-term babies. If nursing mothers do receive an ARB, the baby's blood pressure should be monitored (GPnotebook, 2017).

Although ARBs have a relatively low potential to interact with other drugs, the literature identifies a few possible pharmacokinetic and pharmacodynamic drug interactions. For example, ARBs have been shown to increase plasma lithium concentrations. Further, rifampin has the potential to reduce losartan concentrations; fluconazole reduces the activation of losartan to its active moiety. Both of these interactions may negatively impact the efficacy of losartan. Pharmacodynamically, since an ARB may increase serum potassium levels, combinations with other drugs that may also increase potassium levels may result in hyperkalemia to the point of cardiac arrhythmias. An ARB should not be used concomitantly with ACE inhibitors since these combinations increase the risk of hypotension, hyperkalemia, and renal impairment. Lastly, an ARB should not be combined with the direct renin inhibitor aliskiren (Tekturna) due to an increased risk of kidney failure, hyperkalemia, and excessive hypotension (Medicinenet, 2017).

Wachtell et al. (2008) compared the preventive properties against atrial fibrillation (AF) of a regimen of beta blockers (atenolol) to angiotensin II blockade (losartan). Both regimens were designed to achieve similar reductions in blood pressure. The Losartan Intervention for Endpoint reduction in hypertension (LIFE) study enrolled 8,851 hypertensive patients, as well as patients with left ventricular hypertrophy. Only patients without AF at baseline were enrolled in the trial. The losartan arm enrolled 4,298 patients, while the atenolol cohort included 4,182 patients. The average follow-up time was 4.8 years. The endpoint, new-onset AF, was recorded in 150 patients who received losartan. Of those who received atenolol, 221 suffered AF (p=0.001) despite similar reductions in blood pressure. Regression analysis demonstrated that the occurrence of new-onset AF was an accurate predictor of stroke. Investigators concluded that new-onset AF and associated stroke were significantly reduced by losartan compared to atenolol, despite similar reductions in blood pressure (Wachtell et al., 2005).

Diuretics

One way to lower blood pressure is to induce the body to excrete additional sodium and water, reducing fluid volume. This reduction in the amount of fluid that flows through the blood vessels effectively reduces pressure on blood vessels, countering hypertension (Mayo Clinic, 2017c).

Diuretics are grouped into three distinct categories: thiazide, loop, and potassium sparing. Each type acts on different sites in the kidney and thus has a different use, causing dissimilar adverse event profiles. As a result, each type of diuretic requires unique precautions. The type chosen can be specially tailored for each individual patient to meet his/her specific needs (Mayo Clinic, 2017c).

Thiazide diuretics

Thiazide diuretics, readily available as generic drugs, are often the least expensive medications useful for the treatment of hypertension. Examples include:

- Chlorothiazide (Diuril) – Chlorothiazide is available in tablets of 250 and 500 mg; as powder for reconstitution for parenteral injection of 500 mg; as an oral solution of 250 mg/500 mL (Globalrph, 2017b).
- Chlorthalidone (Hygroton) – Chlorthalidone is available in tablets of 25, 50, and 100 mg (Globalrph, 2017b).
- Hydrochlorothiazide (Microzide) – Hydrochlorothiazide is available in tablets of 25, 50, and 100 mg, in capsules of 12.5 mg and as an oral solution of 50 mg/5 mL (Globalrph, 2017b).
- Indapamide (Lozol) – Indapamide is available in tablets of 1.25 and 2.5 mg (Globalrph, 2017b).
- Metolazone (Zaroxolyn and Mykrox) – Metolazone is available in tablets of 2.5, 5, and 10 mg (Globalrph, 2017b).

Loop diuretics

- Loop diuretics (named for their action at the ascending limb of the loop of Henle in the kidney) are readily available as generic drugs. Loop diuretics include:
- Bumetanide (Bumex) – Bumetanide is available in tablets of 0.5, 1, and 2 mg, and as a solution for intramuscular (IM) or IV injection of 0.25 mg/mL (Globalrph, 2017b).
- Ethacrynic acid (Edecrin) – Ethacrynic acid is available in tablets of 25 and 50 mg, and as powder for reconstitution for parenteral injection of 50 mg (Globalrph, 2017b).
- Furosemide (Lasix) – Furosemide is available in tablets of 20, 40, and 80 mg; as a solution for IV or IM injection of 10 mg/mL; as an oral solution of 8 and 10 mg/mL (Globalrph, 2017b).
- Torsemide (Demadex) – Torsemide is available in tablets of 5, 10, 20, and 100 mg and as a solution for IV injection of 10 mg/mL (Globalrph, 2017b).

Potassium-sparing diuretics

Potassium-sparing diuretics are unique in that they do not promote the secretion of potassium into the urine. Examples include:

- Amiloride (Midamor) – Amiloride is available in tablets of 5 mg (Globalrph, 2017b).
- Eplerenone (Inspra) – Eplerenone is available in tablets of 25 and 50 mg (Globalrph, 2017b).
- Spironolactone (Aldactone) – Spironolactone is available in tablets of 25, 50, and 100 mg (Globalrph, 2017b).
- Triamterene (Dyrenium) – Triamterene is available in tablets of 50 and 100 mg (Globalrph, 2017b).

Potassium-sparing diuretics should be avoided or used with caution in patients with relatively high levels of serum potassium, patients with severe kidney impairment, those with Addison's disease, or those taking ACE inhibitors, an ARB, or aliskiren. Further, patients who use these medications should avoid additional potassium intake, which can be found in many salt substitutes. Pharmacy professionals should emphasize the importance of potassium intake with patients receiving potassium-sparing diuretics. Many patients may be unaware of the potentially dangerous interaction between seemingly innocuous salt substitutes and these drugs (Patient Info, 2017).

Diuretic class effects

Typically, diuretics are well tolerated and can be used safely in most patients. However, side effects have been associated with these medications, including increased levels of urination and a loss of critical minerals. Key parameters to monitor when using these drugs are potassium and sodium. Additional adverse events to be wary of are dizziness, dehydration, headaches, muscular cramps, gout, and impotence (Mayo Clinic, 2017c).

Diuretics are commonly prescribed to treat hypertension both before and during pregnancy. Al-Balas, Bozzo, & Einarson (2009) cited a meta-analysis of nearly 7,000 neonates who were exposed to diuretics during pregnancy. This examination did not record an increased risk of birth defects, fetal growth restriction, thrombocytopenia, or diabetes (Al-Balas, Bozzo & Einarson, 2009).

High doses of diuretics are known to suppress lactation, which may also occur at lower dose levels. Clinicians should monitor the weight of infants of nursing mothers who receive these medications to ensure adequate milk production. The levels of drugs in milk have not been largely assessed, but are thought to be too low to be of significance. Nonetheless, shorter-acting diuretics are the medication of choice and should be used at the lowest dose for the shortest duration, to achieve the intended benefit in the mother. Although insufficient data is available to provide definitive information, eplerenone and spironolactone should be used only in cases where the benefit of these medications outweighs the risk to the fetus (SPS, 2017).

Drug interactions with diuretics are largely limited to those with other drugs impacting potassium excretion, such as carbamazepine and corticosteroids (combination associated with hypokalemia). Diuretics can also result in lithium and digoxin toxicities. Cases of myelosuppression have been reported when methotrexate is used concomitantly with some diuretics. Nonsteroidal anti-inflammatory drugs can decrease the efficacy of diuretics while increasing potassium levels due to reductions in prostaglandin synthesis (Collard, 2001).

Wing et al. (2003) enrolled 6,083 hypertensive patients between the ages of 65 to 84 years in a study designed to compare the observed outcomes in older patients treated with diuretics versus ACE inhibitors. The primary endpoint was the occurrence of cardiovascular events. At baseline, all subjects were well-aligned: 62 percent of each group had received previous treatment. A total of 3,044 patients were randomized to receive treatment with an ACE inhibitor; 3,039 received a diuretic. Subjects were followed for a median duration of 4.1 years. By the end of the study, blood pressure had similarly decreased in both groups. In the ACE inhibitor group, cardiovascular events occurred at the rate of 56.1 per 1,000 patients. Alternately, 59.8 cardiovascular events were recorded in patients who received diuretics (p=0.05). Differences in male subjects were more pronounced (17 percent more likely to have a cardiovascular event, p=0.02), while no differences were observed in females (p=0.98). Investigators concluded that the treatment of older patients with ACE inhibitors is associated with less cardiovascular outcomes than that offered by diuretics alone, especially in men, despite similar effects on hypertension (Wing et al., 2003).

Beta-blockers

Beta-adrenergic blocking agents are medications that block the hormone epinephrine, which sometimes results in reductions of cardiac contractility (both rate and force), leading to reductions in blood pressure. Furthermore, some agents are also capable of blood pressure reduction by causing vasodilation (Mayo Clinic, 2017d).

Beta-blockers are a diverse group of medications that employ a host of pharmacologic properties. Their benefits on mortality and cardiovascular disease in patients with heart failure or acute myocardial infarction is well established. It was thought that beta blockers may provide similar benefit to patients as a first-line treatment for hypertension; however, this benefit is controversial. Recent studies have shown little to no effect on mortality for the treatment of hypertension (Wiysonge, Bradley, Volmink, Mayosi, & Opie, 2017).

Wiysonge et al. (2017) recently published results from a large meta-analysis that examined outcomes from a total of 13 randomized clinical trials. Of these studies, four studies looked at a total of 23,613 patients and compared beta blockers to placebo. Five studies, enrolling 18,241 patients, compared beta blockers to diuretics. Four studies, which were designed to compare calcium channel blockers (CCB) to beta blockers, enrolled 44,825 patients. The final three studies, with 10,828 patients, characterized the difference between beta blockers and drugs that impacted the renin-angiotensin system (RAS). Across all of these trials, a total of 40,245 participants received beta blockers, three-fourths of whom took atenolol. Results

showed no difference in all-cause mortality between the patients who received a placebo and those who had been administered beta blockers, diuretics, or RAS inhibitors. In the CCB comparison, all-cause mortality was seven percent higher in patients who received beta blockers. In the single study that evaluated older patients at least 65 years old, the differences were more pronounced: Atenolol usage was associated with a 63 percent greater incidence of coronary heart disease, compared to patients who received a diuretic. Investigators concluded that current evidence suggested that in the treatment of hypertension, beta blockers have little to no effect on mortality and that these medications are inferior to other antihypertensive drugs (Wiysonge et al., 2017).

Contemporary practice appears to be in step with Wiysonge's (2017) publication: Beta blockers are largely relegated to second-line therapy, as described in JNC 8 (AAFP, 2014). Examples of beta blockers include:

- Atenolol (Tenormin) – Atenolol is available in tablets of 25, 50, and 100 mg, and as a solution for IV of 0.5 mg/mL (Globalrph, 2017c).
- Bisoprolol (Zebeta) – Bisoprolol is available in tablets of 5 and 10 mg (Globalrph, 2017c).
- Metoprolol tartrate (Lopressor), metoprolol succinate (Toprol-XL) – Metoprolol tartrate is available in tablets of 25, 50, and 100, as a solution for IV of 01 mg/mL. Metoprolol succinate is available in tablets of 25 mg, 50 mg, 100 mg, and 200 mg (Globalrph, 2017c).
- Nadolol (Corgard) – Nadolol is available in tablets of 20, 40, 80, 120, and 160mg (Globalrph, 2017c).
- Nebivolol (Bystolic) – Nebivolol is available in tablets of 2.5, 5, 10, and 20 mg (Globalrph, 2017c).
- Propranolol (Inderal LA, InnoPran XL) – Propranolol is available in tablets and capsules of 10, 20, 40, 60, and 80 mg; as suspensions of 4 mg/mL; and as a solution for IV of 1 mg/mL (Globalrph, 2017c).

Beta blockers may be less effective in Black and/or older patients, especially if given as monotherapy (Mayo Clinic, 2017d).

Beta blocker class effects

Common side effects associated with the use of beta blockers include fatigue, cold extremities, and weight gain. Less common adverse events include shortness of breath, insomnia, and depression. Beta blockers can hypothetically trigger asthma attacks and mask signs of hypoglycemia in diabetics. It can also increase serum lipid levels (Mayo Clinic, 2017d).

Based on available data, beta blockers are generally well tolerated and can be used with relative safety during pregnancy. However, beta blockers can cause intrauterine growth retardation if administered during the first month of pregnancy (Joglar & Page, 1999).

The concentrations of beta blockers that partition into breastmilk varies between agents. Some data suggests that atenolol and nadolol may have high affinities to enter breast milk. As a result, other beta blockers may be preferred in these patients (MotherToBaby.org, 2015).

Each beta blocker has a unique pharmacologic profile, which leaves it susceptible to agent-specific drug interactions. Symptomatic interactions with these medications are generally infrequent; however, prescribers need to be familiar with the interaction potential of each agent that they prescribe, relative to existing medications and supplements. Potential drug interactions are numerous and are beyond the scope of this educational program (Blaufarb, Pfeifer, & Frishman, 1995).

Calcium channel blockers

Using calcium channel blockers decreases the entry of calcium into cardiac tissue and blood vessel tissue. The heart rate may decrease as a result, and blood vessels can relax and widen. Both mechanisms lead to decreases in blood pressure (Mayo Clinic, 2016b).

According to JNC 8, calcium channel blockers play a critical role as first-line agents in the treatment of hypertension (AAFP, 2014). A number of calcium channel blockers are available: Some are short-acting; others rely on sustained release formulations to provide a longer effect on blood pressure. Examples include:

- Amlodipine (Norvasc) – Amlodipine is available in tablets of 2.5, 5, and 10 mg (Globalrph, 2017d).
- Diltiazem (Cardizem) – Diltiazem is available in immediate release tablets of 30, 60, 90, and 120 mg; extended/sustained release capsules of 60, 90, 120, 180, 240, 300, and 360 mg; and as a solution for IV of 5 mg/mL (Globalrph, 2017d).
- Felodipine (Plendil) – Felodipine is available in extended release tablets of 2.5, 5, and 10 mg (Globalrph, 2017d).
- Isradipine (Dynacirc) – Isradipine is available in immediate release capsules of 2.5 and 5 mg, and controlled release tablets of 5 and 10 mg (Globalrph, 2017d).
- Nicardipine (Cardene) – Nicardipine is available in immediate release capsules of 20 and 30 mg; sustained release capsules of 30, 45, and 60 mg; and as a solution for IV of 2.5 mg/mL (Globalrph, 2017d).
- Nifedipine (Adalat and Procardia) – Nifedipine is available as immediate release capsules of 10 and 20 mg and extended release tablets of 30, 60, and 90 mg (Globalrph, 2017d).
- Nisoldipine (Sular) – Nisoldipine is available as extended release tablets of 10 mg, 20 mg, 30 mg, and 40 mg (Globalrph, 2017d).
- Verapamil (Isoptin) – Verapamil is available as immediate release tablets of 40, 80, and 120 mg and sustained release tablets of 120, 180, and 240 mg (Globalrph, 2017d).

Calcium channel blockers have been shown to be especially effective in Black and older people, relative to other antihypertensive medications (Mayo Clinic, 2016b).

Although calcium channel blockers are generally safe and well tolerated, adverse events may include constipation, headache, heart palpitations, rash, dizziness, flushing, drowsiness, and nausea (Mayo Clinic, 2016b).

The use of calcium channel blockers is relatively common during pregnancy. A population-based approach determined that while third trimester use was associated with an increased risk of neonatal seizures, jaundice, and hematologic disorders, there was no evidence of an increased risk of congenital anomalies (Alabdulrazzaq & Koren, 2012).

Limited published evidence and clinical experience suggest that nifedipine and verapamil are compatible with breastfeeding. While nicardipine usage is also considered to be appropriate, less clinical experience has been documented. Interestingly, nifedipine is sometimes employed as an off-label remedy for painful nipple spasms in breastfeeding mothers (SPS, 2017).

In addition to the additive effects of calcium channel blockers on other drugs impacting blood pressure, calcium channel blockers are prolific inhibitors of the Cytochrome P450 (CYP) family of isozymes. All calcium channel blockers inhibit CYP2D6 and CYP2C9 to varying degrees. These findings are critical, as some of these drug interactions may be clinically significant. Prescribers must be familiar with the interaction potential of each agent that they prescribe relative to existing medications and supplements. Potential drugs interactions are numerous and are beyond the scope of this educational program (Ma, Prueksaritanont, & Lin, 2000).

Brown et al. (2000) conducted a randomized trial that enrolled 6,321 hypertensive patients between the ages of 55 and 80. Patients received either nifedipine (3,157 patients) or a

hydrochlorothiazide/amiloride combination diuretic product (3,164 patients). Titration was accomplished by doubling the starting dose, as well as the addition of atenolol or enalapril. The primary outcomes of interest were cardiovascular death, myocardial infarction, heart failure, or stroke. The average follow-up time for each group was about 11 years. Primary outcomes were recorded in 6.3 percent of patients who received nifedipine and 5.8 percent in the diuretic cohort of patients. While the overall risk of a primary outcome was 10 percent higher (on average) in the nifedipine group, the difference was not statistically significant (p=0.35). While the impact on blood pressure was similar between treatments (173/99 mmHg at baseline compared to 138/82 mmHg at the end of the study for both groups), there was an eight percent higher study withdrawal rate due to peripheral edema in the nifedipine group compared to the patients who received the diuretic (p<0.0001). Serious adverse events were more frequent in the diuretic group than in the nifedipine patients (880 versus 796, p=0.02). Investigators concluded that nifedipine and diuretic treatments were equally effective in the prevention of cardiovascular and cerebrovascular hypertension complications: Drug choice should be based on tolerability and/or blood pressure response (Brown et al., 2000).

Alpha blockers

By reducing the effect of the hormone norepinephrine, alpha blockers relax the smooth muscles of small blood vessels, allowing them to remain relaxed and less restrictive to blood flow. This ultimately results in a decrease in blood pressure (Mayo Clinic, 2016c).

Although alpha blockers are relatively common in hypertension treatment, they are generally used as second-line agents in cases of difficult-to-control hypertension (Mayo Clinic, 2016c).

A variety of alpha blocker (sometimes called alpha-adrenergic blockers/antagonists, adrenergic blockers, or alpha-blockers) medications are available for the treatment of hypertension and can be short- or long-acting agents. Examples include:

- Doxazosin (Cardura) – Doxazosin is available as tablets of 1, 2, 4, and 8 mg (Globalrph, 2017e).
- Prazosin (Minipress) – Prazosin is available as tablets of 1, 2, and 5 mg (Globalrph, 2017e).
- Terazosin (Hytrin) – Terazosin is available as tablets of 1, 2, 5, and 10 mg (Globalrph, 2017e).

Alpha blocker class effects

A "first-dose effect" is peculiar to some alpha blockers. It results in orthostatic hypotension, a pronounced low blood pressure and dizziness, when these agents' dosages are started. As a result, some patients may faint upon rising to an upright position. Additionally, some patients experience continued orthostatic hypotension after the first dose, which can be of particular importance in elderly patients who are at an increased risk of falling. Due to the risk of orthostatic hypotension with alpha blockers, it is critical that pharmacy professionals make patients aware of this side effect. Proper education should include directions for patients to rise slowly when getting up, the use of judicious caution, and assistance or supervision when available (Mayo Clinic, 2016c).

Potential adverse events associated with the use of alpha blockers include headache, pounding heart, dizziness, weakness, and weight gain. A decrease in low-density lipoprotein (LDL) cholesterol may be a positive side effect of some alpha blockers. Although not definitive, some research has suggested that the use of alpha blockers is associated with an increased risk of heart failure (Mayo Clinic, 2016c).

Although alpha blockers have not been adequately studied in pregnant women, their use in this population is common. Moreover, these agents have been demonstrated to be safe in examinations of pregnant animals. All drugs carry some degree of risk and use in women who are pregnant or who are trying to become pregnant should be evaluated on a patient-specific basis (Semins & Matlaga, 2013).

Alpha blockers should be used cautiously in women with essential hypertension who are breastfeeding, especially in the cases of premature infants and newborns. Other anti-hypertensives are generally better choices than alpha blockers for breastfeeding women (SPS, 2017).

Although clinically significant drug interactions with alpha blockers are not common, there are some combinations that healthcare professionals should be wary of, in addition to the additive effects of combining antihypertensive medications. When used in combination with beta blockers, alpha blocker-mediated first-dose hypotensive effects can be exaggerated. Cimetidine has been shown to enhance the hypotensive effects of tamsulosin due to decreases in its metabolism (Collard, 2001b).

The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) enrolled 42,418 hypertensive patients 55 and older with at least one additional risk factor for cardiovascular disease. Patients received a variety of antihypertensive regimens to assess the long-term effect of heart failure development in high-risk patients. A total of 9,061 patients were assigned to receive doxazosin; 15,256 patients were administered chlorthalidone for a median duration of 3.3 years. Results demonstrated that of the patients who were treated with doxazosin (monotherapy + add-on rescue therapy), participants had twice the overall risk for the development of heart failure than did patients who were randomized to receive chlorthalidone (monotherapy + add-on rescue therapy). Further to that, 68 percent of the doxazosin patients required an additional medication to achieve their target blood pressure. Fifty-nine percent of the chlorthalidone patients needed the extra intervention. Investigators concluded that the diuretic chlorthalidone was significantly more effective than doxazosin at heart failure prevention in high-risk hypertensive patients (Davis et al., 2002).

Alpha-agonists

Alpha agonists cause vasodilation through the stimulation of the central brainstem, resulting in the reduction of blood pressure. Although these agents were originally developed for use as anesthesia adjuncts, early reports showed that when a single dose of clonidine was withheld prior to the onset of anesthesia, acute hypertension resulted (Brodsky & Bravo, 1976). As a result, research focused on the use of these medications as potential hypertension therapies (Brodsky & Bravo, 1976).

In general, these medications carry relatively high potential risks of side effects. As a result, their use is limited. Examples of alpha agonists used in the treatment of hypertension include:

- Clonidine (Catapres) – Clonidine is available as tablets of 0.1, 0.2, and 0.3 mg, as well as transdermal patches, in 0.1mg/day, 0.2mg/day, and 0.3mg/day patches (BI, 2009).
- Methyldopa (Aldomet) – Methyldopa is available in tablets of 125, 250, and 500 mg (Merck, 2004) and as a solution for IV of 50 mg/mL (Medscape, 2017).

Alpha agonists class effects

Side effects associated with the use of alpha agonists include sedation, fatigue, dizziness, impotence, constipation, bradycardia, dry mouth, fever, and headache (Mayo Clinic, 2016d).

Abruptly stopping alpha agonists can result in a sudden, dangerously high blood pressure elevation. As a result, the discontinuation of these medications must be performed with caution. Pharmacy professionals should educate their patients to employ a conservative tapering approach when medical practice requires the discontinuation of these medications (Mayo Clinic, 2016d).

Of all antihypertensive drugs, methyldopa has the longest safety record in pregnant women. It is thus considered the agent of choice for lowering blood pressure in this population without significantly impacting fetal health. It should be noted, however, that there is no sufficient data to assess the impact on fetal health during the first trimester of pregnancy. Clonidine is largely used in the third trimester with no reports of adverse outcomes. Like methyldopa, data are not available to guide clonidine usage during the first trimester.

While methyldopa is compatible with breastfeeding, clonidine should be used with caution. Infants should be monitored for hypotension (SPS, 2017).

When used with other anti-hypertensives, a potentiation of effect should be expected. In addition, patients who receive both methyldopa and lithium should be closely monitored for lithium toxicities. Iron supplements have been shown to reduce the bioavailability of methyldopa. As such, patients receiving methyldopa should not be given iron supplementation; pharmacy professionals should educate those who receive methyldopa to avoid the use of iron supplements (Druglib, 2017). Clonidine is known to potentiate the CNS-depressive impact of alcohol and other sedating drugs. Further, its hypotensive effects can be reduced by tricyclic antidepressant agents. Lastly, clonidine carries the potential for additive cardiac effects, including AV block and bradycardia. As a result, caution is warranted if used concomitantly with drugs known to impact sinus node function (BI, 2009).

Sibai, Mabie, Shamsa, Villar, & Anderson (1990) studied 263 pregnant women with mild hypertension at six to 13 weeks' gestation. Patients were randomized to receive methyldopa, labetalol, or placebo in roughly similar numbers. All patients were followed throughout their pregnancy, receiving renal function assessments as well as fetal status checks. There were no significant differences in blood pressure, gestational age, or laboratory results at baseline. Assessed outcomes included the occurrence of preeclampsia, abruptio placentae, or pre-term delivery. As expected, patients treated with anti-hypertensive medications maintained lower blood pressures throughout their pregnancies compared to the placebo group. With regard to the outcomes, there was no significant difference between any of the treatment groups. Moreover, there were no differences between groups for gestational age at delivery, incidence of fetal growth retardation, birth weight, or head circumference. Of note, in addition to one stillbirth in each of the treatment groups, there was one miscarriage in the methyldopa group. Investigators concluded that management of maternal blood pressure in the case of pregnant women with mild hypertension did not affect perinatal outcomes (Sibai et al., 1990).

Renin inhibitors

Renin inhibitors offer a novel approach to the treatment of hypertension through direct inhibition of renin's catalytic activity—the initial and rate-limiting step in the renin-angiotensin system. Renin inhibitors offer a more complete blockade of this system than any other known modality; therefore, possibly offering a greater protection from hypertensive complications with a relatively benign side effect profile (Shafiq, Menon, & Victor, 2008). As a result, blood vessels relax and dilate, allowing increased blood flow and reductions in blood pressure. It is important to note that renin inhibitors, ARBs, and ACE inhibitors all target the same metabolic process, just at different points (WebMD, 2017b).

Currently, only one renin inhibitor, known as aliskiren (Tekturna), has received FDA authorization for marketing in the United States. It is available as 150 and 300 mg tablets (Novartis, 2010).

Adverse events associated with aliskiren

Side effects commonly observed with aliskiren include stuffy nose, dizziness, diarrhea, and headache. Rarely (but more seriously), allergic reactions have occurred that can lead to hives, difficulty breathing, and swelling of the face, lips, tongue, and/or throat. All healthcare professionals who care for patients receiving aliskiren should be aware of the potential allergic reactions associated with its use. Pharmacy professionals should advise their patients to be vigilant in monitoring for these potentially serious adverse events. Pharmacy professionals should also include instructions to immediately contact their prescriber or call 911, as appropriate, should they occur. (WebMD, 2017).

Although there is no clinical experience with aliskiren in pregnant women, it is known that agents that act on the renin-angiotensin system can lead to fetal morbidity and mortality. If a woman who takes aliskiren becomes pregnant, the drug should be discontinued as soon as possible (Novartis, 2010).

Although it is not known if aliskiren is excreted into human breast milk, it is secreted into the milk of lactating rats. Since the potential for adverse effects on a nursing infant is not known, prescribing this agent in nursing mothers must be determined based on an individualized risk/benefit assessment (Novartis, 2010).

Aliskiren depends on the CYP3A isoenzyme system for metabolism. Further, aliskiren employs the p-glycoprotein efflux system. These two properties subject aliskiren to a number of drug-drug interactions with concomitant medications. Interactions with ketoconazole, cyclosporine, verapamil, and atorvastatin all resulted in clinically significant increases in patient exposure to aliskiren, potentially resulting in excessive hypotensive effects. Although aliskiren does not modulate major CYP isoenzymes, a clinically significant drug-drug interaction was demonstrated with furosemide (furosemide levels decreased by 30 to 50 percent) (Novartis, 2010).

The literature contains descriptions of two large studies designed to assess the long-term impacts of aliskiren. The first in type 2 diabetic patients with chronic kidney disease, cardiovascular disease, or both. The second trial was designed to determine if the addition of aliskiren to ACE inhibition therapy provided a benefit to patients with chronic heart failure.

Parving et al. (2012) conducted a study that enrolled 8,561 type 2 diabetic patients with chronic kidney disease, cardiovascular disease, or both. Patients were administered either a placebo or aliskiren as adjunct therapy to either an ACE inhibitor or ARB. The primary endpoint was the time to cardiovascular death; MI; stroke; hospitalization for heart failure; end-stage renal disease; death due to kidney failure; kidney transplant; or a doubling of serum creatinine. The trial ended after the completion of the secondary interim analysis, which occurred after a median follow-up period of 32.9 months. Despite significantly greater blood pressure reductions in patients randomized to aliskiren, the primary endpoint at this point had occurred in 18.3 percent of patients randomized to aliskiren and 17.1 percent of placebo patients. Further, the incidence of hyperkalemia was higher in the treated group than with the placebo (11.2 percent versus 7.2 percent). Investigators concluded that the addition of aliskiren to standard of care treatment (ACE inhibitor or ARB) in type 2 diabetics at high risk of cardiovascular and/or renal events is

not supported. In fact, the authors stated that the addition of aliskiren may be harmful in this population (Parving et al., 2012).

McMurray et al. (2016) accomplished a clinical evaluation in patients with heart failure and a reduced ejection fraction (ATMOSPHERE). A total of 2,236 patients were assigned to receive once-daily doses of enalapril alone, 5-10 mg; 2,340 received aliskiren 300 mg once daily, and 2,340 received combination therapy (both medications). On average, treatment persisted for 36.6 months. The primary outcome of interest in the study was death due to a cardiovascular event or hospitalization for heart failure. The primary outcome occurred in 770, 791, and 808 patients in the combination, aliskiren, and enalapril groups, respectively. These observed differences were not statistically significant. Nonetheless, higher frequencies of hypotension, elevated creatine and potassium levels were observed in the combination group. Investigators concluded that the addition of aliskiren to ACE inhibition therapy in heart failure patients with reduced ejection fraction led to an increased rate of adverse events, without providing significant increases in efficacy (McMurray et al., 2016). increased rate of adverse events, without providing significant increases in efficacy (McMurray et al., 2016).

Combination products

The treatment of hypertension can be challenging in some cases. At times, patients will require more than one medication in order to reach their blood pressure targets. There is some evidence that the assembly of a fixed dose combination drug product to treat hypertension confers certain advantages. These advantages may include enhanced efficacy, improved patient compliance, cost, convenience, safety, and even an increased patient perception of wellness (Lewanczuk & Tobe, 2008).

Combination therapy to combat hypertension is required in about 75 percent of patients. Choosing a rational therapy begins with the selection of a combination of agents that exhibit additive blood pressure reductions and a high degree of tolerability, as well as a demonstrated ability to reduce cardiovascular endpoints in long-term clinical trials. Drugs that are most typically employed in combination are low-dose diuretics, ACE inhibitors, ARBs, and calcium channel blockers. In treatment-resistant hypertension, mineralocorticoid antagonists (spironolactone or eplerenone) can be especially effective. Strategies for combination therapy continuously evolve. Recent studies support the initial implementation of combination products, with documentation of faster attainment of goals and improved long-term outcomes (Gradman, 2012). JNC 8 guidelines allow the initiation of treatment with a combination product if medically indicated (AAFP, 2014).

Choosing an initial hypertension treatment agent

It has been long established that there is a therapeutic benefit to lowered blood pressure that employs a variety of approaches, ranging from lifestyle changes to scores of available pharmacotherapeutic agents that rely on a variety of different mechanisms of action. Although clinicians should work to help their patients achieve their blood pressure targets, their ultimate goal should be to reduce the incidence of the morbidity and mortality associated with hypertension. Outcome studies have been conducted that documented the long-term benefits of a number of categories of drugs (for example, diuretics, ACE inhibitors, and calcium channel blockers). While it is good to know that these medications provide benefits to hypertensive patients, prescription optimization requires a critical knowledge of how one category of drugs acts relative to another. For example, while JNC 8 suggests initially starting a patient on a diuretic, ACE inhibitor, ARB, or calcium channel blocker (except in some special populations), the guidance does not specify which agent to use. In some cases, the relative value of newer, more expensive medications prescriptions can play a critical role.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was a large randomized trial designed to characterize the impact that first-line drugs have on preventing fatal coronary heart disease (CHD) or myocardial infarction (MI) in high-risk, hypertensive patients. Sponsored by the National Heart, Lung and Blood Institute (NHLBI) the study enrolled 9,000 to 15,000 subjects per treatment cohort, with a follow-up period of four to eight years. Subjects were randomized to receive antihypertensive treatments with a calcium channel blocker (amlodipine), an ACE inhibitor (lisinopril), an alpha-blocker (doxazosin), or a diuretic (chlorthalidone) (Furburg et al., 2002). Interim analysis demonstrated that treatment with chlorthalidone was significantly superior to doxazosin at an interim analysis. As a result, the doxazosin treatment cohort was terminated early (Davis et al. 2002).

Excluding patients randomized to receive doxazosin, the study enrolled 33,357 hypertensive patients 55 years of age and older with at least one other risk factor for CHD. A total of 15,255 patients were randomized to receive chlorthalidone 12.5-25 mg/day; 9,048 patients were assigned to the amlodipine 2.5-10 mg/day group; and 9,054 patients were administered lisinopril 10-40 mg/day. The primary outcome of interest was fatal CHD or non-fatal MI. Outcomes of secondary interest included stroke, all-cause mortality, non-fatal CHD, and a variety of events related to cardiovascular disease. On average, patients were followed for 4.9 years: Primary outcomes occurred in 2,956 patients with no significant differences recorded between treatment groups. The six-year risk rate was 11.5 percent, 11.3 percent, and 11.4 percent for chlorthalidone, amlodipine, and lisinopril, respectively. Similarly, there was no difference in all-cause mortality across treatment groups. With regard to secondary outcomes, results were similar with the exception of heart failure. For this outcome, the six-year risk rates of occurrence for the amlodipine and chlorthalidone were 10.2 percent and 7.7 percent, respectively. Examination of six-year risks for combined cardiovascular disease, stroke, and heart failure also showed a significant advantage to chlorthalidone when compared to lisinopril. ALLHAT investigators concluded that thiazide diuretics are superior to ACE inhibitors, calcium channel blockers, and alpha blockers. Further, they are generally less expensive, and thus should receive preference as the first-step agent for antihypertensive therapy (Furburg et al., 2002).

Gestational hypertension

Similar to primary and secondary hypertension, the basis of gestational hypertension is increased blood pressure. However, there are differences in these pathologies: The treatment of gestational hypertension is directed by a different set of guidelines. The primary objective in the treatment of pregnant women is the prevention of more worrisome conditions—including placental abruption or fetal growth restriction. Further, the treatment plan must consider the health of the unborn baby in addition to the wellbeing of the mother (Weber, 2017). The most commonly employed treatment options for gestational hypertension are:

- Bed rest: Crowther, Bouwmeester, & Ashurst (1992) conducted a prospective study designed to characterize the impact of bedrest on both pregnant women with hypertension, as well as in their offspring. Investigators studied 218 pregnant women with hypertension during their final trimester. Study participants were randomized to either remain at home and receive routine outpatient care, or to be admitted to the hospital. While hospitalized women were encouraged to rest in bed, they were allowed voluntary ambulation around the hospital ward. The other cohort (control group) was encouraged to maintain normal activities at home. Disease progression was defined as: The development of severe hypertension (≥160/110 mmHg); proteinuria; need for labor induction; or pre-term delivery. Fetal outcomes were assessed by birthweight, number of infants who were small for gestational age (SGA), the need for admission to the neonatal intensive care unit, and their length of hospitalization. While the rate of severe hypertension development was reduced in the hospital rest group by 53 percent, there was no impact on fetal growth or neonatal morbidity (Crowther, et al., 1992).
- Pharmacotherapy: Omole & Akanji (2010) argued that gestational hypertension can result in damage to the blood vessels of both the expectant mother, as well as placental blood supply to the fetus. In order to best guide the treatment of these patients, they conducted a retrospective study to characterize the pharmacotherapeutic approach to the management of hypertension in pregnancy at a secondary hospital. To this end, they reviewed the case notes of 300 randomly selected cases of pregnant hypertensive patients between the ages of 15 and 40. Their analyses showed that the most common pharmacological intervention was methyldopa, followed by nifedipine and hydralazine. While patients responded to all of these medications, thus resulting in shorter admissions (relative to treatment received), these differences were not statistically significant (Omole & Akanji, 2010). Unfortunately, since this investigation did not include a control group, it is impossible to conclude the impact of pharmacological intervention. In addition, investigators did not include fetal health as an outcome.

Weber (2017) acknowledges that drug therapy is an effective approach to moderating gestational hypertension, noting the importance of selecting and administering the medications with the safety of both the mother and the fetus in mind. Further, Weber states that drug therapy is typically employed only in cases of severe hypertension, that is > 150/110 mmHg. Lastly, clinicians should be aware that while all drug use confers risk, labetalol, methyldopa, and nifedipine may be the best choices based on extensive experience, safety, and tolerability profiles for both mother and fetus (Weber, 2017).

Hypertensive emergency

When severe hypertension (diastolic blood pressure > 120 mmHg) is accompanied by signs of organ damage (in the brain, kidneys, and/or the cardiovascular system), a hypertensive emergency must be considered. Specific organ damage may include encephalopathy, left ventricular failure, pulmonary edema, myocardial ischemia, aortic dissection, and renal failure. Damage to organs can progress rapidly, often leading to death. It is critical to note that while some patients who suffer from stroke or intracranial hemorrhage present with elevated blood pressure, these increases are often a consequence of the condition rather than a cause (Bakris, 2017).

The signs and symptoms of a hypertensive emergency include diastolic blood pressure > 120 mmHg. Central nervous system (CNS) symptoms include rapidly changing neurologic abnormalities, such as confusion, blindness, and seizures. Cardiovascular symptoms include chest pain and dyspnea. Renal damage can be asymptomatic or can include signs of severe azotemia, such as lethargy or nausea (Bakris, 2017).

Hypertensive emergencies are ideally treated in an intensive care setting. Blood pressure should be evenly reduced. Abrupt lowering of blood pressure may be detrimental. Typical agents for blood pressure reduction vary, depending on the target organ for treatment. Goals for blood pressure reduction are generally on the order of 20 to 25 percent per hour, with titration based on symptoms. The medication chosen should be a short-acting, IV drug that can be easily titrated (Bakris, 2017). Typical first-line drugs are listed below:

- Nitroprusside (Nipride) – Nipride, available as a solution for IV of 25 mg/mL, is considered to be the most effective parenteral agent for the majority of hypertensive emergencies. It is extremely fast acting (within seconds) and lasts for only two to three minutes, making it an ideal candidate for titration. The typical dose is 3 µg/kg/minute, and the maximum dose is 10 µg/kg/minute. A downside of Nipride is its associated risk of cyanide and thiocyanate toxicity, especially in renally impaired patients or after prolonged treatment (Globalrph, 2017f).
- Fenoldopam (Corlopam) – Corlopam, available as a solution for IV of 10 mg/mL, is a vasodilator that is as effective as nitroprusside. An additional advantage is that it also increases renal blood flow six times as potently as dopamine and is not associated with the accumulation of toxic metabolites. While Corlopam can be used in all hypertensive emergencies, it is of a particular benefit in patients who suffer from renal insufficiency. Its onset of action is five to 10 minutes and its duration is approximately one hour. A typical starting dose is 0.1 to 0.3 3 µg/kg/minute, with a maximum dose of 1.6 3 µg/kg/minute (Globalrph, 2017f).
- Labetalol (Trandate) – Trandate, available as a solution for IV of 5 mg/mL, is the only beta blocker useful in treating hypertensive emergencies. Trandate, which does not increase heart rate, is also safe to use in patients with active coronary disease. Trandate should typically be avoided in patients with asthma, COPD, CHF, and bradycardia of heart block. Its onset of action is five to 10 minutes, with a duration of two to six hours, and peak effects in about 30 minutes. The initial infusion rate is 0.5 – 2 mg/min (Globalrph, 2017f).
- A study by Tumlin et al. (2000) enrolled 94 patients who suffered from hypertensive emergency (to include a sustained diastolic blood pressure of at least 120 mmHg and evidence of target organ damage) into a trial where they received 0.01, 0.03, 0.1, or 0.3 mg/kg/min fenoldopam for 24 hours. The primary endpoint was the extent of reduction in diastolic blood pressure in each of the three higher dose groups relative to the lowest-dose group. Diastolic blood pressure decreased in a dose-dependent fashion, with significant differences observed between the low-dose group and the 0.1 and 0.3 mg/kg/min groups. Treatments were well tolerated, and no deaths or serious adverse events were reported. All patients were transitioned to oral or transdermal antihypertensive agents without incident. Investigators concluded that fenoldopam was capable of safely and effectively lowering blood pressure in a dose-dependent fashion in patients who suffered from hypertensive emergencies (Tumlin et al., 2000).

Conclusion

According to current guidelines, a sustained blood pressure that exceeds 120/80 mmHg warrants patients to incorporate an awareness of blood pressure and implement lifestyle changes to prevent hypertension. When blood pressures exceed 129/80 mmHg, patients are diagnosed with type 1 hypertension. Clinicians should act to lower these patients' blood pressures to a safer level. Depending on other risk factors, this may include the use of medications. Although nearly one-third of American adults are hypertensive, 20 percent of these patients are not properly diagnosed. Positive lifestyle changes should be the cornerstone of all hypertension treatment regimens, although a number of medications are also available to help patients meet their blood pressure goals. All patients and medications must be considered individually in order to make optimal treatment choices. Prescribers should also consider the results of large outcome-based clinical investigations. It appears that there is a relative parity between some medication classes' ability to manage blood pressure and impact meaningful outcomes. Although both alpha blockers and beta blockers are effective in blood pressure reduction, there is a lack of long-term outcome data to support the use of these medications. Further, although direct renin inhibitors have the potential to impact the treatment of hypertension, there is no adequate long-term data to support their use to date. Each patient must be considered individually in order to make suitable medication choices, and in many cases, clinicians should consider diuretics for first-line therapy.

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Final Examination Questions

Select the best answer for each question and then proceed to **EliteLearning.com/Book** to complete your final examination.

51. While there is no obvious cause of primary hypertension, a number of pathologies may result in secondary hypertension. Which of the following are potential causes of secondary hypertension?
    a. Pregnancy.
    b. Conditions impacting the kidney.
    c. Conditions impacting the heart.
    d. All of the above.

52. Regardless of the cause of hypertension, proper treatment involves maintaining a proper balance between which of the following two properties?
    a. Fluid intake and output.
    b. Cardiac output and resistance to blood flow.
    c. Sympathetic and parasympathetic nervous systems.
    d. None of the above.

53. Which of the following statements regarding elevated blood pressure (according to current ACC guidelines) is TRUE?
    a. Elevated blood pressure begins at 110/70mmHg.
    b. Patients with elevated blood pressure are at risk of developing hypotension.
    c. These patients should embrace lifestyle changes.
    d. Patients are in a hypertensive crisis when blood pressures are less than 140/90mmHg.

54. Which of the following statements regarding the prevalence of hypertension in the United States is TRUE?
    a. Approximately 20 percent of people who suffer from hypertension are not diagnosed properly.
    b. Nearly half of Americans with hypertension have received proper diagnosis.
    c. Only 25 percent of Americans with hypertension require medication for proper management.
    d. Less than 20 million health care visits in 2009 involved the treatment of hypertension.

55. Which of the following lifestyle changes are NOT associated with positive effects on hypertension?
    a. Weight loss.
    b. Excessive alcohol consumption.
    c. Consumption of healthy foods.
    d. Increased activity.

56. In addition to the capability of lifestyle changes to reduce hypertension, which of the following changes to the cardiovascular system are NOT anticipated to be modulated by exercise and weight loss?
    a. Decreases in arterial stiffness.
    b. Improvements in endothelial function.
    c. Decreases in left ventricular mass/wall thickness.
    d. Increases in cardiac contractility.

57. The JNC 8 provides a number of evidence-based guidelines for the proper treatment of hypertension. In addition to general clinical practice approaches (applicable to most patients), JNC 8 specifically calls out treatment differences for which of the following populations?
    a. Native Americans.
    b. Jewish patients of Eastern European descent.
    c. Black populations.
    d. Vikings.

58. The JNC 8 is a consensus document designed to provide hypertension treatment guidelines. Which of the following statements regarding JNC 8 is TRUE?
    a. In general, initial interventions should always be a monotherapy.
    b. In Black populations, most initial interventions should include a diuretic or a calcium channel blocker.
    c. After therapy commences, it is critical to wait at least two months before altering the regimen.
    d. ACE inhibitors are contraindicated in patients with chronic kidney disease.

59. Identify a class adverse event associated with the use of ACE inhibitors.
    a. Dry cough.
    b. Increased libido.
    c. Enhanced taste.
    d. Hypokalemia.

60. Which of the following statements regarding ACE inhibitors is FALSE?
    a. These medications are capable of relaxing blood vessels.
    b. Their activity is based on an inhibition of an enzyme involved in the generation of angiotensin II.
    c. These medications have no drug-drug interaction potential.
    d. Dry cough is a known adverse event associated with these agents.

Course Code: RPFL03MH

Chapter 5: Pharmacy Law

3 Contact Hours

By: Debra A. Notturno-Strong, RPh, MS, MSA

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Learning objectives

After completing this course, the learner will be able to:

- Explain the reasons for and provisions of the Federal Food and Drug Act of 1906.
- Explain the differences between an adulterated and a misbranded drug.
- Identify significant Federal Food, Drug, and Cosmetic Act amendments affecting pharmacy practice.
- Explain the five classes of controlled substances.
- List the requirements for ordering and dispensing controlled substance medications.
- Describe the implications of the Combat Methamphetamine Epidemic Act and the Anabolic Steroids Control Act.
- Identify the effects of federal legislation on pharmacy operations and practice, including the Poison Prevention Packaging Act of 1970, and biosimilars.
- Explain the scope and implications of the Prescription Drug Marketing Act.
- Identify the mandated requirements associated with Omnibus Budget Reconciliation Acts of 1990 and 1993.
- Describe the patient privacy and pharmacy implications of the Health Insurance Portability and Accountability Act.

Introduction

Pharmacy is, by far, the most regulated profession in health care. Pharmacists have a professional obligation to be aware of the history and development of laws and regulations and the implications to practice and patient care. Beginning with the Federal Food, Drug, and Cosmetic Act of 1938 (FDCA), which has been amended numerous times since its passing, federal drug legislation has distinguished between prescription and over-the-counter medications and established that drugs must be both safe and effective, must be properly labeled, and must be manufactured and stored under sanitary conditions. In addition, the Controlled Substances Act (CSA), by using advances in technology, such as electronic prescribing and the Automation of Reports and Consolidated Orders System, has expanded regulatory oversight and scheduling of medications to minimize diversion, misuse, and abuse. Federal legislation has been enacted to combat methamphetamine abuse, deter tampering with medications, ensure patient privacy, mandate patient counseling – the list goes on. The intent of this course is to provide in-depth information on the FDCA and CSA, as well as an overview of the federal laws that affect how pharmacy is practiced.

The first chapter of this course provides an overview of the FDCA and its associated amendments. The second chapter focuses on the CSA. The third chapter addresses various federal laws that affect pharmacists and pharmacy practice.

CHAPTER 1: OVERVIEW OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT AND ASSOCIATED AMENDMENTS

The foundation for federal law begins with the U.S. Constitution. Laws result from legislative enactments, called statutes, and are enacted by Congress. The federal government is one of limited powers; federal statutes may be enacted only in those areas specifically delegated to Congress in the U.S. Constitution. Federal authority to regulate drugs can be found in the Interstate Commerce Clause of the U.S. Constitution. State legislatures can also enact laws. State authority to regulate is derived from the 10th Amendment to the U.S. Constitution and under its inherent police powers. State laws play a significant role in the practice of pharmacy by defining requirements and the scope of pharmacy practice. Conflicts generally exist when state law is less strict than federal law. When federal and state law conflict, federal law will preempt state law under the Supremacy Clause of the U.S. Constitution.

Since 1906, federal law has played a significant role in the practice of pharmacy. The Federal Food, Drug, and Cosmetic Act of 1938 (FDCA) has been amended numerous times over the last 80 years (FDCA, 2013). Most amendments were enacted as a response to a significant event that caused death or endangered lives. The goal of the amendments is to protect the health, safety, and welfare of patients and consumers.

This chapter discusses the significant amendments to the FDCA that changed the face of pharmacy practice.

FEDERAL FOOD AND DRUG ACT OF 1906

Historically, the Federal Food and Drug Act of 1906 is known as the Pure Food and Drug Act; this act served as an important precursor to the FDCA and was passed following concern over unsafe and unsanitary practices and products in the food and drug industries. At the time, no law permitted the federal government to inspect processing facilities, and consumers were concerned with the purity of products. The Pure Food and Drug Act created what is known today as the U.S. Food and Drug Administration (FDA). It provided authority for federal inspection of meat products and prohibited adulterated or misbranded food or drugs from interstate commerce. The act fell short because it did not extend to cosmetics, did not grant authority to ban unsafe drugs, and did not require labels on products to identify ingredients. In addition, false statements made by a drug manufacturer were not considered misbranding, Once passed, the FDCA superseded the Pure Food and Drug Act (FDA, 2015b).

FDCA DEFINITIONS OF KEY TERMS

Section 321 of the FDCA defines important terms necessary to fully comprehend the intent of the law and its amendments. Three of these terms are as follows.

Drug

The FDA defines the word *drug* as a substance:

- Recognized by an official pharmacopoeia or formulary.
- "Intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease".
- "Intended to affect the structure or any function of the body".
- Intended for use as a component of a medicine but not as a device or a component, part, or accessory of a device.

(FDCA, 2013)

Cosmetic

The FDCA defines cosmetics as "articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body for cleansing, beautifying, promoting attractiveness, or altering the appearance" (FDCA, 2013). Among the products included in this definition are skin moisturizers, perfumes, lipsticks, fingernail polishes, eye and facial makeup preparations, cleansing shampoos, permanent waves, hair colors, and deodorants, as well as any other substance intended for use as a component of a cosmetic product.

Device

A device, according to the FDCA, is "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is recognized in the official National Formulary, or the U.S. Pharmacopoeia, or any supplement to them." A device is:

- "Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals.
- Intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes".

(FDCA, 2013)

THE FDCA

In 1938, the FDCA, which created the FDA as we know it, replaced the Pure Food and Drug Act following the 1937 therapeutic disaster of sulfanilamide elixir. Sulfanilamide, one of the first sulfa drugs, was available in tablet and powder form and was marketed as a wonder drug because of its effectiveness in treating a range of bacterial infections. When southern states demanded a liquid formulation for children, the manufacturer, Massengill, found the powder dissolved readily in the solvent diethylene glycol (the chemical analog of antifreeze). The untested elixir caused more than 100 fatalities, mostly children (Mason, Leavitt, & Chaffee, 2012).

Under the Federal Food and Drug Act of 1906, the FDA did not have the authority to withdraw the drug from the market. The public outcry was intense. To prevent events like the sulfanilamide deaths from happening again, the FDCA came to fruition. The FDCA set forth guidance requiring all drugs and devices to be labeled with adequate directions and to have been determined to be safe and effective for use before they are introduced into interstate commerce. The FDCA also required food and cosmetics to be safe and properly labeled.

The act specifically mandated that the safety of all drugs be proved by the manufacturer to the FDA before marketing. Drugs marketed before 1938 were exempted from new drug status, meaning the manufacturer did not have to submit safety data to the FDA; thus, those agents were grandfathered and allowed to remain in commerce. Drugs in this category include levothyroxine, phenobarbital, and ergotamine.

The FDCA also enhanced regulatory oversight for therapeutic claims made by manufacturers and further clarified the definitions of misbranding and adulteration. A drug is considered adulterated if it:

- Was prepared, packed, or held in unsanitary conditions that could have allowed it to become contaminated.
- Was exposed to a container that may have been contaminated it.
- Contained any filthy, putrid, or decomposed substance.
- Purported to be a drug in an official compendium but its strength differed from or its quality fell below standards, unless the difference was explained on the label.
- Was not in a compendium and its strength differed from or its quality fell below that which was represented.
- Was mixed or packed with any substance that reduced its strength or quality, or had been wholly or partly substituted.
- Was manufactured under conditions that did not conform to current good manufacturing practice.

(GMP; FDCA, 2013)

GMP is a set of regulations that established minimum requirements for the methods, facilities, or controls used in the manufacture, processing, packaging, or holding of a drug product.

A drug or device is considered misbranded if any of the following situations occurs:

- The drug or device label was false or misleading in a way that may confuse the consumer.
- The labeling failed to state the name and place of business, the quantity of each active drug, the generic name and any proprietary name of the drug; adequate directions for use (including quantity, frequency, duration, time, route for use, and preparation necessary for use); warnings the layperson can understand; and an expiration date.

- The drug or device was subject to deterioration, unless its label bears appropriate precautionary statements.
- It was health endangering if used in the manner suggested on the label.
- The manufacturer was not registered with the FDA and the drug was not listed as manufactured by the manufacturer.

(FDCA, 2013)

AMENDMENTS TO THE FDCA

Durham-Humphrey Amendment of 1951

The debate that followed the passing of the FDCA concerned determining which drugs could be used safely by the patient and which drugs would require a prescription. This was sorted out in the Durham-Humphrey Amendment of 1951 (DHA), also known as the Prescription Drug Amendment. The legislators who cosponsored the bill were pharmacists: Hubert Humphrey (who would later serve as U.S. vice president, under President Lyndon B. Johnson, in the 1960s) worked as a pharmacist in father's pharmacy in South Dakota before finishing his doctorate and entering politics in Minnesota, and Carl Durham was a pharmacist representing North Carolina. Before this amendment, the manufacturer of the drug decided whether the drug would be made available without a prescription. Therefore, for the same drug, one manufacturer could claim over-the-counter (OTC) status while another claimed prescription status. The DHA created two classes of medications: prescription (legend) and nonprescription (OTC). Under the DHA, a drug is considered available through prescription if only safe to use with professional medical advise and supervision, and the new drug application (NDA) says it is prescription only.

The DHA also required any drug that was habit forming or potentially harmful must be dispensed under the supervision of a physician as a prescription drug and labeled with the statement "Caution: Federal law prohibits dispensing without a prescription." This label is frequently called the federal legend warning, which is the origination of the term *legend drugs*. Within this legislation, provisions were established to authorize oral prescriptions and refills of prescription drugs by the prescriber or an authorized agent (state law permitting). The DHA provides the authority for a practitioner to prescribe prescription drugs; however, the term *practitioner* is determined by state licensure. It is the responsibility of the pharmacist to ascertain appropriate prescriptive authority and the scope of practice allowed by law. The labeling requirements set forth in the amendment for prescription drugs included the following:

- Name and address of the dispenser.
- Serial number and date of prescription or of its filling.
- Name of the prescriber.
- Name of patient.
- Directions for use and cautionary statements.

Originally, the drug name and strength were not required. Labeling requirements for OTC drugs included the following:

- Manufacturer name and address.
- Name and quantity of the drug.
- Active and inactive ingredients.
- Purpose and indications for use.
- Directions for use and warning statements.

The DHA authorized the FDA to switch prescription drugs to OTC status by regulation when conditions warranted. Those conditions include a request by the manufacturer through supplemental application to its approved NDA, a petition to the FDA, or a request generated by the FDA directly. If the switch is driven by the manufacturer, it is possible for a product to be OTC and an identical product from a different manufacturer to be available only with a prescription. A widely recognized example is Flonase nasal spray manufactured by GlaxoSmithKline. The company received approval for an OTC version, Flonase Allergy Relief, in 2014; however, generic fluticasone propionate is available by prescription only.

Kefauver-Harris Amendments of 1962

The Kefauver-Harris Amendments of 1962, also known as the Drug Efficacy Amendments, were prompted by another therapeutic disaster. The sedative thalidomide had been marketed in Europe in the late 1950s and was hailed as a wonder drug that could treat various maladies (Thalidomide Victims Association of Canada, 2017). Of the many uses, thalidomide was found to be highly effective in treating morning sickness in pregnant women and gained appeal as a nonbarbiturate sleep aid. The product was advertised as safe even during pregnancy. The drug was banned in March 1962 amid mounting reports of severe birth defects in babies. Thalidomide was never approved for distribution in the United States because of the perseverance and tenacity of an FDA inspector, Dr. Frances Kelsey. Kelsey was concerned about the lack of information regarding clinical trials taking place in the United States that did not require FDA approval or federal oversight (Fintel, Samaras, & Carias, 2016). As it was, there was no requirement to report ill effects during these trials.

The Kefauver-Harris Amendments changed all that and were enacted in direct response to the thalidomide tragedy. The amendment established tighter restrictions regarding the surveillance and approval process for drugs to be sold in the United States. It also established the requirement for manufacturers to submit an NDA. The NDA process requires manufacturers to provide sufficient information for the FDA to determine that the drug is safe and effective when used as instructed, the benefits outweigh any risks, the labeling and the package insert are appropriate and complete, and manufacturing complies with GMP. This amendment created extensive controls for clinical investigations requiring informed consent and reporting of adverse drug reactions.

In addition, the new law required the FDA to assess the efficacy of all drugs introduced since 1938 and transferred the regulation of prescription drug advertising from the Federal Trade Commission to the FDA. This transfer allowed drug advertising to be more closely regulated, established GMP by the drug industry, and granted the FDA greater powers to access company production and control records to verify GMP compliance (FDA, 2017).

Medical Device Amendments of 1976

Until 1976, the FDA lacked controls or authority over medical devices. Much like prior amendments, the Medical Device Amendments (MDAs) emanated from concerns about public health and safety (S. 510, 1976), particularly claims regarding the intrauterine contraceptive device the Dalkon Shield. The shield was implanted in more than 2.5 million women over a 4-year period and was reportedly responsible for a fivefold increase in pelvic inflammatory disease (Kolata, 1987). However, what distinguishes the Dalkon Shield from thalidomide is that there may be various causes for pelvic inflammatory disease, whereas the birth defects caused by thalidomide were uncommon and consistent. The MDAs created three classes of medical devices, according to their function: (1) a requirement that all devices achieve premarket testing, review, and approval; (2) the establishment of performance standards to provide reasonable assurance of safety and efficacy: and (3) the establishment of mandatory manufacturing methods that require the importer, manufacturer, or distributor to maintain detailed records.

Subsequent guidance provides the FDA with authority to reclassify a device, the requirement to report death or serious injury related to a device, and the latitude to seize devices in the event of reports concerning unreasonable risk or harm.

In July 2016, the FDA finalized guidance exempting "general wellness products" from pre- and postmarket regulatory requirements. The FDA defined general wellness products as those intended to encourage healthy activity and how it relates to helping reduce the risk of chronic diseases in conditions. Devices in this category include exercise equipment, fitness trackers, and mobile applications that track heart rate and blood pressure (Mehzer, 2016).

Orphan Drug Act of 1983

The Orphan Drug Act of 1983 was a congressional response to pharmaceutical industry concerns that the current drug approval process was too costly to develop drugs for rare diseases or conditions. Rare diseases or conditions are defined as occurring in less than 200,000 people in the United States or 200,000 or more people in the United States if the probability that the cost of developing the drug will not be recovered from sales (FDA, 2013). For example, developing drugs for Huntington's disease, myoclonus, amyotrophic lateral sclerosis or Lou Gehrig's disease, Tourette syndrome, and muscular dystrophy is not financially beneficial and thus undesirable to pharmaceutical companies. The Orphan Drug Act specifically encourages the development of these therapies if the drug fills an unmet medical need, defined as providing a therapy where none exists or providing a therapy that may be potentially better than the available therapies. The provisions of the Orphan Drug Act include adoption of key early access and expedited approval programs from the FDA: priority review (1987 and 1992), fast-track review (1988), and accelerated approval (1992). Priority review is when a drug offers a significant therapeutic advantage; fast-track facilitates drug development and expedites review of clinical trials, forgoing Phase 3; and accelerated approval is when a drug demonstrates a positive therapeutic effect or benefit in clinical trials that, based upon scientific data, may provide some clinical benefit, such as a drug that shows evidence of shrinking tumors.

The law provides several incentives for research and development that include the following:

- Seven years of market exclusivity or protection from market competition.
- Eligibility for grants to support product development.
- Tax credits for clinical research and trials.
- Application fee waivers.
- Assistance with trial design.

Drug Price Competition and Patent Term Restoration Act of 1984

The Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the Hatch-Waxman Act, amended both FDCA and patent laws as signature legislation to enhance competition between brand and generic pharmaceutical companies (S. 2926, 1984). The act was intended to strike a balance between patent exclusivity and innovating generic drug development.

Designed to encourage competition, a significant piece of this legislation was the development of the abbreviated new drug application (ANDA) process. The Hatch-Waxman Act changed the rules, allowing generic manufacturers to demonstrate that their generic drug product is simply bioequivalent to an approved brand-name drug, allowing bioequivalence testing to occur before the brand product patent expires, and creating the incentive for 180 days of exclusively for the first manufacturer to submit a successful ANDA. This means that the first company to receive generic product approval would have 6 months on the market before another generic is allowed to enter.

However, the implications of the Hatch-Waxman Act have the potential to limit the pharmaceutical pipeline and stifle innovation (Kesselheim 2011). Historically, patents provided brand manufacturers with the opportunity to recoup the costs associated with bringing a drug from research, through development, and to the market. New drug development, according to the Pharmaceutical Research Manufacturers of America (PhRMA), involves the screening of between 5,000 and 10,000 compounds, which can take, on average, 10 to 15 years, costing as much as $1.3 billion. The time, money, and effort spent on research and development do not guarantee clinical success and FDA approval (PhRMA, 2016).

Thus, for brand manufacturers, the Hatch-Waxman Act rewarded technological advances by defining patent extensions to be 100% approval time plus 50% (or up to 5 years) of testing time, for an extension of no more than 14 years. It also set a timeframe for nonpatent exclusivity, meaning the NDA data were kept as proprietary by the FDA: the manufacturer was given 5 years of data exclusivity for new chemical entities (excluding salts or esters) and 3 years of exclusivity for improvements to approved brand products (new uses, dosage form, and regimens) provided through clinical trials. The act also set the procedures for patent challenges.

As part of the act, the FDA was required to produce a list of approved generic products with monthly supplements. *Approved Drug Products with Therapeutic Equivalence Evaluations,* or the Orange Book, was first published in 1979 and became an official part of the federal mandate. In keeping with advances in digital technology, the FDA has gone mainstream with the Orange Book Express, a comprehensive iOS and Android application that is updated monthly and provides critical information on equivalence, NDA and ANDA approvals, and patent and exclusivity material.

Safe Medical Devices Act of 1990

The Safe Medical Devices Act of 1990 strengthened the MDAs of 1976 by increasing the information the FDA and manufacturers receive regarding serious problems with medical devices. The act required user facilities and manufacturers to report deaths and serious injuries that may have been contributed to or caused by the device, to maintain adverse event files, to adopt a method of device tracking, and to conduct postmarket surveillance for certain devices introduced after January 1, 1991. Accordingly, pharmacy professionals that routinely handle and/or dispense medical devices (e.g., ambulatory infusion pumps) should be aware of their obligations to comply with this act.

Dietary Supplement Health and Education Act of 1994

Before 1994's Dietary Supplement Health and Education Act (DSHEA), Congress enacted the Nutrition Labeling and Education Act of 1990, empowering the FDA to restrict the dietary supplement industry by requiring supplements to bear nutrition labeling and FDA-approved health claims (S. 784, 1993). In addition, this act gave the FDA the authority, under the food additive provisions of the FDCA, to declare a supplement ingredient unsafe or inadequately tested. In 1994, Congress enacted DSHEA, which defined dietary supplements as foods rather than drugs. The law changed the FDA's role in regulation while outlining a narrow set of claims that dietary supplement manufacturers are permitted to make. The act restricts the FDA's premarket authority and allows dietary supplement manufacturers to evaluate the safety and labeling of products before marketing. The FDA has the authority to approve substantiated health claims.

Through DSHEA, Congress reduced the strong grip that the FDA traditionally had on dietary supplements. Specifically, manufacturers of dietary supplements do not have to prove their product is safe or effective or meet quality standards for strength and purity. Because the FDA does not fully evaluate claims, the following disclaimer must be visible on the label: "This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease" (S. 784, 1993). If a product did not contain this label, it would be subjected to the misbranding provisions of the FDCA.

The act also gives considerable latitude to dietary supplement manufacturers with regard to removal of their products from the marketplace. Unlike drugs, for which the manufacturer must prove the safety of an agent, the FDA must prove a dietary supplement is unsafe before action can be taken to remove it from the market. Therefore, it is important that pharmacists educate patients on appropriate supplement choices and product selection. Pharmacists should be familiar with any state laws specific to these products and be aware of product quality and labeling requirements.

Shortcomings to DSHEA were addressed in the Dietary Supplement and Nonprescription Drug Consumer Protection Act of 2006. This act requires manufacturers to record and report any serious and nonserious adverse events for dietary supplements and nonprescription drugs marketed with an application. It also requires dietary supplement manufacturers to comply with current GMP to assure products are not adulterated or misbranded. Pharmacists should ensure they direct patients to supplements that conform to U.S. Pharmacopeia or National Formulary standards when providing recommendations.

Food and Drug Administration Modernization Act of 1997

The Food and Drug Administration Modernization Act of 1997 (FDAMA) is widely viewed as a sweeping set of FDCA amendments intended to improve the regulation of food, drugs, devices, and biological products. In initiating this legislation, Congress sought to reform the FDA by streamlining the approval process to ensure timely availability of products to benefit the public, to continue to spur innovation and development, and to enhance collaboration between the agency and manufacturers (FDA, 2018). The FDAMA represents a multitude of initiatives and new programs directed at expediting patient care.

Prescription medications

For prescription drugs, the FDAMA aims for the following:

- Accelerating review of important new medications for drugs intended for serious or life-threatening diseases through expedited review.
- Establishing an expanded database on clinical trials accessible by patients.
- Authorizing scientific panels to review clinical investigations.
- Requiring manufacturers to provide patients with advance notice if they plan to discontinue a drug on which patients depend for life support or sustenance or for treatment of a serious or debilitating disease or condition.
- Increasing patient access to experimental drugs and medical devices.

Medical devices

The FDAMA presents the following initiatives for medical devices:

- Allowing priority review and fast-track review for breakthrough technologies in medical devices.
- Targeting resources on medical devices that present the greatest risks to patients.
- Providing the FDA with the authority to contract with outside experts to conduct the initial review of all class I and low-to-intermediate risk class II devices.
- Directing the FDA to focus its postmarket surveillance on higher risk devices.
- Requiring the implementation of a reporting system that concentrates on a representative sample of user facilities – such as hospitals and nursing homes – that experience deaths and serious illnesses or injuries linked with the use of devices.

Manufacturer benefits

The FDAMA directed substantial legislation beneficial to manufacturers, including the following:

- Modernizing of the regulation of biological products by bringing them in harmony with the regulations for drugs and eliminating the need for an establishment license application.
- Eliminating the batch certification and monograph requirements for insulin and antibiotics.
- Streamlining the approval processes for drug and biological manufacturing changes.
- Reducing the need for environmental assessment as part of a product application.
- Expanding the right of manufacturers to disseminate to peer-reviewed journal articles off-labeled indications so long as the company commits to filing a supplemental application to establish safety and efficacy.

Compounded medications

The FDCA provided additional provisions in Section 503A regarding the compounding of medications. In short, the act provided that "a pharmacy is exempt from misbranding, CGMP [current GMP] and new drug requirements if the compounded product met a list of conditions" that includes the following:

- Valid prescription.
- Limited quantity.
- Not a commercially available product.
- Compounded in compliance with U.S. Pharmacopeia.
- Use of approved ingredients.
- Not more than 5% of total prescriptions dispensed.

The compounding provisions highlight continued struggles between the FDA and pharmacies. Because Section 503A was tied to restrictions on advertising, this part of the act met with legal opposition and was never fully enacted. The later section on compounding quality (the "Drug Quality and Security Act of 2013" section) provides additional information.

Food and Drug Administration Amendments Act of 2007

The Food and Drug Administration Amend-ments Act of 2007 (FDAAA) reauthorized the 1992 Prescription Drug User Fee Act, which allows the FDA to collect fees from drug companies to help fund reviews of new drugs (FDA, 2015a). FDAAA enabled shorter review times and a more predictable review process while maintaining high-quality reviews. It also reauthorized the 2002 Medical Device User Fee and Modernization Act allows for user fees and allows the FDA to make significant improvements in the medical device review program; the 2002 Best Pharmaceuticals for Children Act, which encourages more studies in children and promotes the development of treatments for children; and the 2003 Pediatric Research Equity Act, which continues the FDA's authority to require studies in children concerning certain medical products and under other specific circumstances. In addition, the FDAAA mandates the expansion of the national clinical trials data bank, ClinicalTrials.gov, to include expanded information on clinical trials and their results and provides the FDA with additional requirements, authorities, and resources with regard to both pre- and postmarket drug safety (FDA, 2015a).

A substantial, and frequently criticized part of the FDAAA is the establishment of risk evaluation and mitigation strategies (REMSs). The FDA can require REMSs to ensure that the benefits of a drug outweigh its risks. Those risks include serious infection, severe allergic reaction, liver damage, or severe birth defects. REMSs may be required by the FDA as part of the approval process of a new product or for an approved product if new safety information arises. REMSs should be viewed as safety strategies that to enables patients to have continued access to these types of medicines by managing their safe use (FDA, 2017a). As of October 2017, the REMSs program has 71 medications with specific guidance designed for the individual risks for each drug (FDA, 2017a). The FDA created a website for patients and providers to access the latest postmarket drug safety information.

The FDAAA addressed direct-to-consumer advertisements, giving the FDA the authority to determine whether advertisements are clear, conspicuous, and neutral regarding side effects and contraindications of drugs. The FDA may make recommendations to include changes that are necessary to protect consumer health and well-being or consistent with prescribing information for the product under review and can make statements for inclusion in the advertisement to address the specific efficacy of a drug as it relates to specific population groups, including the elderly, children, and racial and ethnic minorities, if appropriate and if such information exists.

Drug Quality and Security Act of 2013

The Drug Quality and Security Act of 2013 (DQSA) was a direct federal response regarding the safety of compounded drugs. It was prompted by the 2012 multistate outbreak of fungal meningitis and other life-threatening infections resulting from contaminated steroid injections manufactured by the New England Compounding Center in Framingham, Massachusetts (DOJ, 2014). The outbreak was responsible for 753 cases of infection with at least 64 deaths across 20 states (CDC, 2015). Much like the other amendments to the FDCA, the intent of the law is to protect patients from unsafe, ineffective, and poor-quality compounded drugs. The act is composed of two parts: Title I that addresses drug compounding and Title II that relates to drug supply chain security.

Title I creates a new section to the FDCA, allowing compounders of sterile drugs to register as an outsourcing facility. An outsourcing facility does not have to be a licensed pharmacy. To comply with Title I, the entity:

- Must compound under the supervision of a licensed pharmacist or physician.
- May or may not obtain patient-specific prescriptions.
- May use only drugs from a bulk ingredients list.
- Must comply with current GMP.
- Is not allowed to compound products already commercially available unless the products are on shortage.
- Must undergo regular FDA inspections on a risk-based schedule.
- Must submit information about products compounded within the facility to the FDA every 6 months.
- Must report product-related adverse events to the FDA.
- Must pay an annual fee of $15,000 to the FDA to cover inspection costs (FDA, 2017b).

The act sets forth a mechanism of communication for state boards of pharmacy and the FDA, concerning any warning letters or sanctions imposed at the local level to compounding medications, and establishes a recall process should quality become an issue.

The DQSA also reinstates portions of Section 503A of the FDAMA, whereby a traditional compounder, defined as a licensed pharmacist or licensed physician, is exempt from current GMP, labeling, or drugs with adequate directions for use and the need for approval of drugs under NDAs or ANDAs.

Title II of the DQSA focuses on drug supply chain security. Specifically, Title II mandates the development of a national track-and-trace electronic system for prescription medications to protect consumers from potentially harmful drug exposures and contaminations such as those experienced with the New England Compounding Center. The act calls for verification of the legitimacy of a drug product down to the individual package level, enhanced detection of illegitimate drug products in the supply chain, and improved drug product recall mechanisms. As of January 2015, dispensers, manufacturers, repackagers, third-party logistics providers, and wholesale distributors must ensure that trade partners are authorized by the FDCA, provide lot-level product tracing information, and establish a system for verification and handling of suspect or illegitimate products.

CONCLUSION

This chapter highlighted the historical federal legislative actions that continue to shape pharmacy, pharmacy practice, and pharmaceutical manufacturing while advancing patient care and safety. The foundation of the Food, Drug and Cosmetic Act continues to be strengthened by amendments that have specifically addressed misbranding and adulteration of products, prescription and over-the-counter medications, labeling requirements, and provisions for the FDA to establish a New Drug Application program, to have authority over medical devices, and to provide incentives for the development of orphan drugs.

The establishment of the Abbreviated New Drug Application program opened the door for generic manufacturers to prove their product was bioequivalent, thereby bringing more cost-effective products to the market faster. It also rewarded brand manufacturers for technological advances, recognizing the time and money associated with new drug discovery and research and development.

These important changes were followed by efforts to accelerate the availability of drugs to treat serious diseases – fast-track review and the development of risk evaluation and mitigation strategies. Compounding issues came to the forefront, with the need to protect the patient taking center stage. The Food Drug and Cosmetic Act continues to evolve and echo the importance of medication safety, patient safety, and transparency in government programs.

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CHAPTER 2: COMPREHENSIVE DRUG ABUSE PREVENTION AND CONTROL ACT OF 1970

The federal Controlled Substances Act (CSA), as part of the Comprehensive Drug Abuse Prevention and Control Act of 1970, provides the regulatory foundation for manufacturing, distribution, use, and scheduling of narcotics, stimulants, depressants, hallucinogens, anabolic, steroids, and other chemicals. This chapter discusses how controlled substances are scheduled and rescheduled, prescription requirements, corresponding responsibility, how to identify red flags when presented with a prescription, proper disposal, and recordkeeping requirements.

COMPREHENSIVE DRUG ABUSE PREVENTION AND CONTROL ACT OF 1970

The Comprehensive Drug Abuse Prevention and Control Act of 1970 is composed of three titles:

- Title I – Rehabilitation for Drug Abusers.
- Title II – CSA.
- Title III – Importation and Exportation, Criminal Forfeiture, and Drug Law Amendments.

This discussion focuses on Title II (the CSA), the requirements associated with it, and the authority to enforce it.

FEDERAL CSA OF 1970

The CSA, enacted in 1970, was implemented as part of Title 21 of the Code of Federal Regulations. The processes outlined in the CSA represent what has been called a closed system of distribution, which means maintaining accountability for all controlled drugs at every step – manufacture, wholesale distribution, retail or institutional dispensing, and sale to the end user. The U.S. Drug Enforcement Administration (DEA), formed in 1973, is responsible for implementing and enforcing the CSA. The DEA works in partnership with state and local entities to ensure controlled substances are not being diverted for illegal use.

State laws may differ from federal laws; however, the more stringent law has precedence. As an example, the CSA does not place specific restrictions on time limits from date of issue or quantity limit for Schedule II controlled substances. Guidance is detailed in state controlled substances laws.

The CSA places all substances that are regulated under federal law into one of five schedules. Placement is based upon the substance's medical use, potential for abuse, and safety or dependence liability (Schedules of Controlled Substances, 2016).

Schedule I

Schedule I substances are defined as follows:

- The drug or other substance has a high potential for abuse.
- The drug or other substance has no currently accepted medical use in treatment in the United States.
- There is a lack of accepted safety for use of the drug or other substance under medical supervision.

A partial listing of Schedule I substances include heroin, lysergic acid diethylamide (LSD), marijuana (cannabis), peyote, methaqualone, and 3,4-methylenedioxymethamphetamine (Ecstasy).

Schedule II

Schedule II substances meet the following criteria:

- The drug or other substance has a high potential for abuse.
- The drug or other substance has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions.
- Abuse of the drug or other substances may lead to severe psychological or physical dependence.

Examples of Schedule II narcotics include hydromorphone (Dilaudid), methadone (Dolophine), meperidine (Demerol), oxycodone (OxyContin or Percocet), and fentanyl (Sublimaze or Duragesic). Other Schedule II narcotics include morphine, opium, codeine, and hydrocodone. Examples of Schedule II stimulants (sometimes identified as Schedule IIN) include amphetamine (Dexedrine or Adderall), methamphetamine (Desoxyn), and methylphenidate (Ritalin). Other Schedule II substances include amobarbital, glutethimide, and pentobarbital.

Schedule III

Substances are placed under Schedule III when they meet the following criteria:

- The drug or other substance has a lower potential for abuse than the drugs or other substances in Schedules I and II.
- The drug or other substance has a currently accepted medical use in treatment in the United States.
- Abuse of the drug or other substance may lead to moderate or low physical dependence or high psychological dependence.

Examples of Schedule III narcotics include products containing not more than 90 mg of codeine per dosage unit (Tylenol with Codeine) and buprenorphine (Suboxone). Examples of Schedule III nonnarcotics (sometimes labeled as Schedule IIIN) include benzphetamine (Didrex), phendimetrazine, ketamine, and anabolic steroids such as Depo-Testosterone.

Schedule IV

Schedule IV substances are defined as follows:

- The drug or other substance has a low potential for abuse relative to the drugs or other substances in Schedule III.
- The drug or other substance has a currently accepted medical use in treatment in the United States.
- Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule III.

Examples of Schedule IV substances include alprazolam (Xanax), carisoprodol (Soma), clonazepam (Klonopin), clorazepate (Tranxene), diazepam (Valium), lorazepam (Ativan), midazolam (Versed), temazepam (Restoril), and triazolam (Halcion).

Schedule V

Substances are placed under Schedule V when they meet the following criteria:

- The drug or other substance has a low potential for abuse relative to the drugs or other substances in Schedule IV.
- The drug or other substance has a currently accepted medical use in treatment in the United States.
- Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule IV.

Examples of Schedule V substances include cough preparations containing not more than 200 mg of codeine per 100 mL or per 100 g (Robitussin AC or Phenergan with Codeine), pregabalin (Lyrica), and atropine/diphenoxylate (Lomotil).

How controlled substances are scheduled and rescheduled

The attorney general is responsible for the enforcement of the CSA and may initiate proceedings to change a drug's schedule or add or remove any drug from a certain schedule. Scheduling, rescheduling, or other changes may be initiated through new legislation. Suggested amendments to the CSA can be made by petition of various interested parties, including the manufacturer of a drug, a medical society or association, a pharmacy association, a public interest group concerned with drug abuse, a state or local government agency, an individual citizen, or by the U.S. Department of Health and Human Services (HHS) through the U.S. Food and Drug Administration (FDA) to the attorney general through the DEA. The DEA is charged with collecting the necessary data through the HHS. Specifically, the DEA administrator requests a scientific and medical evaluation and recommendation from the HHS as to whether the drug or other substance should be controlled or removed from control. The HHS, in turn, requests information from the FDA, evaluations and recommendations from the National Institute on Drug Abuse, and if deemed appropriate, information from the scientific and medical community. The HHS compiles and conveys the information to the DEA with a recommendation as to whether the drug should be controlled and in what schedule it should be placed. Altogether, the attorney general and the HHS must consider eight areas of significance:

1. Scientific evidence of the pharmacological effect of the drug or substance.
2. State of current scientific knowledge regarding the drug or substance.
3. Any risk to public health the drug or substance might pose.
4. Psychic or psychological dependence liability.
5. Whether the drug or substance is an immediate precursor of an already-controlled substance and any related medical considerations.
6. Substance's actual or relative potential for abuse.
7. Its history or current pattern of abuse.
8. Scope, duration, and significance of abuse.

(Schedules of Controlled Substances, 2016)

If the HHS recommends a drug not be controlled, the attorney general must comply. The DEA may not control the substance. However, if the attorney general finds that a drug must be placed into Schedule I to avoid danger to the public, the attorney general may schedule the drug without consulting the secretary of the HHS. Should a manufacturer submit a new drug application to the HHS for any drug that has a stimulant, depressant, or hallucinogenic effect on the central nervous system, this information must be provided to the attorney general if it appears that the drug has the potential for abuse. While the DEA cannot control a substance, the DEA may begin an investigation of a drug at any time based upon information received from law enforcement laboratories, state and local law enforcement and regulatory agencies, or other sources of information.

A substantial change to the CSA was the rescheduling of hydrocodone combination products in 2014 from Schedule III to Schedule II, which significantly affected prescribing and patient access (Throckmorton, 2014). The move imposed upon all hydrocodone combination products the restrictions associated with prescribing Schedule II agents: no refills; a new prescription required monthly except in cases of chronic pain, when the prescriber can provide several prescriptions with an earliest fill date; and no faxing or telephoning of prescriptions to the pharmacy. For patients who were effectively treated with and used hydrocodone combination products appropriately, the change affects the ease and convenience of treatment, especially in chronic pain.

The process to schedule a drug can be complicated and time consuming. Two medications reclassified as Schedule IV from noncontrolled include carisoprodol (Soma) in 2012 and tramadol in 2014. In the case of carisoprodol, the DEA initiated the request to schedule the drug in March 1996. In February 1997, the FDA Drug Abuse Advisory Committee determined the data available did not support the change. The National Institute on Drug Abuse and the College of Problems of Drug Dependence requested pharmacological studies of carisoprodol abuse potential. The DEA continued to gather actual abuse and law enforcement encounters involving the drug. New information was provided to the HHS in November 2005. In October 2009, after a review of the evidence regarding the eight factors, the HHS recommended that carisoprodol be placed in Schedule IV (DEA, 2011). The rule was not enacted until 2012, which illustrates the complexity of the process.

Ironically, state governments have the authority to and may choose to reclassify controlled substances provided that their law is more stringent. The National Association of State Controlled Substances Authorities provides an in-depth profile of each state and any DEA exceptions. In general, many states have chosen to advance the schedule of an agent, for example, from Schedule IV to Schedule III, or to include an agent, such as all butalbital-containing products and codeine cough syrups, in a state controlled substances act. The most recent and prevalent state action is the movement of gabapentin in some states from noncontrolled to Schedule IV.

The debate over schedules is represented in the controversy over the medical benefits of marijuana, which is an area of difference between federal and state drug control laws. More than 35 states have passed some sort of legislation authorizing the use and sale of marijuana for medical purposes. Personal use of marijuana has been decriminalized in at least 18 states and legalized in 10 states (Smith, 2017). Marijuana remains in Schedule I of the CSA and thus is illegal in accordance with

federal law. Given the precedence of the stricter law prevailing, state laws are in violation of federal law.

Before January 2018, the Department of Justice operated under guidance issued in 2013 that identified eight enforcement priorities, deferring the right to challenge but setting the expectation that states that have legalized marijuana will "implement strong and effective regulatory enforcement systems" (DOJ, 2013). According to the memo, the eight areas of concern are as follows:

1. Preventing the distribution of marijuana to minors.
2. Preventing revenue from the sale of marijuana from going to criminal enterprises, gangs, and cartels.
3. Preventing the diversion of marijuana from states where it is legal under state law in some form to other states.
4. Preventing state-authorized marijuana activity from being used as a cover or pretext for the trafficking of other illegal drugs or other illegal activity.
5. Preventing violence and the use of firearms in the cultivation and use of marijuana.
6. Preventing drugged driving and the exacerbation of other adverse public health consequences associated with marijuana use.
7. Preventing the growing of marijuana on public lands and the attendant public safety and environmental dangers posed by marijuana production on public lands.
8. Preventing marijuana possession or use on federal property.

(DOJ, 2013)

In January 2018, Attorney General Jeff Sessions directed the rescission of the policy memos and the restoration of the rule of law enacted by Congress, which prohibits the cultivation, distribution, and possession of marijuana (DOJ, 2018).

Registration

As part of the closed system, the CSA re-quires those who manufacture, distribute, or dispense a controlled substance, or who propose to engage in any of these activities, to register with the attorney general. Those required to register include any business that imports or exports a controlled substance; a manufacturer of a controlled substance; a distributor of a controlled substance; pharmacies that dispense controlled substances; health practitioners that prescribe, administer, or dispense controlled substances; and any person that conducts research or chemical analysis with a controlled substance (Rannazzisi, 2008).

The CSA provides for three categories of exemptions: (1) an agent or employee of any registered manufacturer, distributor, or dispenser of any controlled substance if the person is acting in the usual course of business or employment, which would include a pharmacist employed by a registered pharmacy; (2) a common or contract carrier whose possession of the controlled substance is in the usual course of business or employment, which would include wholesale or manufacturer workers and delivery personnel; and (3) an ultimate user who possesses such substance for a lawful purpose (CSA, 2016).

An individual practitioner may use the registration of their employer to administer or dispense, but not prescribe, controlled substances. Likewise, an individual practitioner employed by a hospital or other institution may administer, dispense, and prescribe controlled substances under the registration of the hospital or institution if the dispensing, administering, or prescribing is done in the usual course of professional practice; if the individual practitioner is authorized by the state in which he or she is practicing; if the hospital or other institution has verified that the practitioner is permitted to dispense, administer, or prescribe drugs within the state; and if the practitioner is acting within the scope of employment in the hospital or institution. The institution authorizes an intern, resident, or foreign-trained physician to dispense or prescribe under the hospital registration and designates a specific internal code number for that individual; and the institution makes those codes available for the purpose of verifying prescribing authority (Food and Drugs, 1973). As an example, if the hospital DEA registration is AB 1234567, a resident prescribing a controlled substance would use the hospital DEA plus an internal code, such as AB1234567-012.

This provision also allows practitioners in the armed services, public health service, or bureau of prisons who are authorized to prescribe, dispense, or administer controlled substances in the usual course of their official duties to use the registration of the facility in which they are assigned.

While the appropriate use of a facility DEA registration with an assigned suffix is lawful, if community pharmacists have questions concerning the validity of the prescriber, they must contact the institution to verify the code.

Disposal of controlled substances

Disposal of controlled substances in the CSA was amended by the Secure and Responsible Drug Disposal Act of 2010 in September 2014. Before this, there were few opportunities for patients (called ultimate users) to dispose of unwanted, expired, or unused controlled substances, because pharmacies, physician's offices, hospitals, and so on were prohibited from taking them back. The only feasible options available for patients were to flush them, throw them away, or continue to store them. These limited options raised environmental concerns and heightened risk for abuse, misuse, diversion, and accidental ingestion of controlled substances. This act gave the DEA authority to establish three options for disposal: registered collection sites with a DEA-authorized medicine collection receptacle (e.g., Medsafe), mail-back programs, and takeback events. In an effort to expand the opportunities for patients to dispose of unwanted medications safely and securely, the DEA permitted retail pharmacies, hospitals, and clinics with onsite pharmacies; manufacturers; distributors; reverse distributors; and narcotic treatment centers, as well as local law enforcement agencies, to register as authorized collectors (DEA, 2016). Collectors distributing mail-back packaging must have an onsite method of destruction or partner with a reverse distributor or law enforcement agency. Collectors are required to document inventories. For mail-back packages and packages awaiting destruction, the collector must record the date of inventory, number of mail-back packages, and unique identifier on each package on hand. Collectors using a collection receptacle (e.g., Medsafe) must record the date of inventory, number and size of liners, and unique identifier of each inner liner for each unused liner and those awaiting destruction.

Storage and security requirements

All applicants and registrants must generally "provide effective controls and procedures to guard against theft and diversion of controlled substances." DEA regulations require all applicants and registrants to comply with specific security standards for storage of controlled substances based upon the category of their registration. As an example, nonpractitioners must store Schedule I and II substances in electronically monitored safes, steel cabinets, or vaults that meet or exceed certain specifications, whereas licensed practitioners must store controlled substances in a securely locked, substantially constructed cabinet and must notify the DEA of the theft or

significant loss of any controlled substances within 1 business day of discovering such a loss or theft.

All registrants are prohibited from hiring employees who have been convicted of a drug-related felony or who have had a DEA registration denied or revoked. DEA regulations also recommend that registrants carefully screen individuals before hiring them as employees to ensure that job applicants do not have convictions for crimes and have not engaged in unauthorized use of controlled substances.

Pharmacies have the option of storing controlled substances listed in Schedules II to V in a locked cabinet or concealing them by dispersal throughout their stock of noncontrolled substances. Federal regulations do not specifically define locked cabinet construction; the intent of the law is that controlled substances must be adequately safeguarded. Some factors considered when evaluating a practitioner's controlled substances security are as follows:

- Number of employees, customers, and/or patients who have access to the controlled substances.
- Location of the registrant (high- or low-crime area).
- Use of an effective alarm system.
- Quantity of controlled substances to be kept on hand.
- Prior history of theft or diversion.

Recordkeeping

Maintaining complete and accurate records for controlled substances, is an essential and significant responsibility in the practice of pharmacy. Each registered pharmacy is required maintain records of all transactions of controlled substances purchased, received, distributed, dispensed, and disposed. Poor recordkeeping and documentation practices are considered violations of the CSA and subject to criminal prosecution.

According to the DEA *Pharmacists Manual* (2010), the records that must be maintained by a pharmacy include the following:

- Executed and unexecuted official order forms (DEA Form 222) or the electronic equivalent.
- Power of attorney authorization to sign order forms.
- Receipts and/or invoices for controlled substances in Schedules III to V.
- All inventory records of controlled substances, including the initial and biennial inventories, dated as of beginning or close of business.
- Records of controlled substances distributed (e.g., sales to other registrants, returns to vendors, and distributions to reverse distributors).
- Records of controlled substances dispensed (e.g., prescriptions and Schedule V logbook).
- Reports of theft or significant loss (DEA Form 106), if applicable.
- Inventory of drugs surrendered for disposal (DEA Form 41), if applicable.
- Records of transfers of controlled substances between pharmacies.
- DEA registration certificate.
- Self-certification certificate and logbook (or electronic equivalent) as required under the Combat Methamphetamine Epidemic Act of 2005.

Inventories and records for Schedule I and II controlled substances must be maintained separately from all other records of the pharmacy. Paper prescriptions must be maintained at the registered location in a separate prescription file.

For drugs and substances listed in Schedules III to V, inventories and records must be maintained either separately from all other records of the pharmacy or in a way that the information is readily retrievable. Paper prescriptions for controlled substances in Schedules III to V may be maintained in a separate prescription file or in a way that they are readily retrievable from the other prescription records of the pharmacy. The term *readily retrievable* means the prescription is stamped in red ink in the lower right corner with a letter C that is no less than 1 inch high and filed with prescriptions for controlled substances listed in Schedules I and II or with the consecutively numbered prescription file for noncontrolled substances. This requirement is waived if the pharmacy uses a computer application that allows timely retrieval of original documents. While computerized records may be maintained off the premises, records must be readily retrievable and capable of being printed upon request from the DEA, law enforcement, or the state board of pharmacy. Electronic copies of prescription records must be sortable by prescriber name, patient name, drug dispensed, and date filled. These records must be kept for 2 years and may be inspected by the DEA or the state board of pharmacy (CSA, 2016).

Inventory Requirements

The initial inventory of all controlled substances must be taken on the opening date of the business. An inventory of all controlled substances on hand is required every 2 years. This biennial inventory may take place on any date provided it is within 2 years of the previous biennial inventory. This requirement is further governed by state law with regard to when the biennial inventory should take place.

The initial inventory record must include the following:

- Date of the inventory.
- Whether the inventory was performed at the start or close of the business day.
- Name of each controlled substance that was inventoried.
- Finished dosage form of each controlled substance.
- Number of dosage units of each finished dosage form in the commercial container.
- Number of commercial containers of each finished dosage form.
- Count of each controlled substance.

In general terms, all inventories must:

- Contain a complete and accurate record of all controlled substances on hand on the date of inventory.
- Be maintained in written, typewritten, or printed form at the registered location.
- Be transcribed promptly if inventory was taken using an oral recording device.
- Include all controlled substances on hand if they are under the possession of the registrant.
- Be accomplished for each registered location.

Inventory counts for Schedule II substances must be exact, but counts for Schedules III to V may be estimated. If the container holds more than 1,000 tablets or capsules and is open, an exact count must be accomplished. If controlled substances are stored at an unregistered, alternate location, the inventory of those items will be included in that of the registered location. If a noncontrolled substance is added to a schedule of controlled substances, an inventory of all stock on hand must be accomplished before the effective date and included in the inventory. Federal law does not mandate any type of daily or perpetual inventory; any such requirements are defined within state regulations. These records must be file separately and be readily retrievable upon request of the DEA or the state board of pharmacy.

Reporting theft or significant loss of controlled substances

Theft and significant loss of controlled substances, regardless of schedule (I to V), must be reported immediately upon discovery to the local authorities and to the closest DEA office. Reports of loss are accomplished on DEA Form 106. The form must be completed within 1 business day. The form may be filled out manually; it is also available online at http://www.deadiversion.usdoj.gov.

Ordering controlled substances

The CSA, through the DEA, established the Controlled Substance Ordering System (CSOS) that allows a purchaser to securely order Schedule I to V controlled substances electronically without a paper DEA Form 222. The materialization of secured technology provides ordering freedom, faster transactions, accurate orders, and decreased costs, in addition to providing timely patient care. Electronic ordering also decreases the number of errors in filling out DEA Form 222, increases the ability for pharmacists to order more frequently without concerns of a more than 72-hour turnaround time, and decreases overall on-hand inventory. The process and steps are as follows (DEA, n.d.):

- An individual enrolls with the DEA and, once approved, is issued a personal CSOS certificate.
- The purchaser creates an electronic Form 222 order using an approved ordering software. The order is digitally signed using the purchaser's personal CSOS certificate and then transmitted to the suppliers. The paper Form 222 is not required for electronic ordering.
- The supplier receives the purchase order and verifies that the purchaser's certificate is valid with the DEA. In addition, the supplier validates the electronic order information just like it would a paper order.
- The supplier completes the order and ships it to the purchaser. Any communications regarding the order are sent electronically.
- The order is reported by the supplier to Form DEA within 2 business days.

The use of technology requires a significant investment, which many pharmacies may not employ for the ordering of Schedule I and II controlled substances. Substances listed in Schedules III to V may be ordered electronically through wholesale distributors and do not require CSOS-enabled software.

Schedule I and II controlled substances, if not ordered electronically through CSOS, must be ordered on DEA Form 222. The form is available only through the DEA and is serially numbered for accountability purposes. The form is completed in triplicate, with Copies 1 and 2 submitted to the supplier and Copy 3 retained by the ordering entity. Upon delivery of the order, Copy 1 is maintained by the supplier and Copy 2 is sent to the agent in charge of the DEA in the area. The ordering entity will document receipt of the items on Copy 3 and maintain the completed DEA Form 222 with their inventory. If the DEA Form 222 is not completed properly, is illegible, is not prepared or signed properly, or shows any alteration, erasure, or change of description, the order will not be filled and Copies 1 and 2 will be returned to the requestor. Upon the return, the requestor is required to void the form and keep it on file.

Report of transactions

The CSA requires all DEA registrants who manufacture and distribute controlled substances to report all transactions to the DEA. This report is accomplished through an automated, comprehensive drug reporting system, the Automation of Reports and Consolidated Orders System (ARCOS), which monitors current and historical records of selected controlled substance inventories and transactions from the point of manufacture, to sale, to distribution and dispensing. The system is used to identify diversion of controlled substance into unauthorized channels of distribution. The drugs monitored through ARCOS include all controlled substances in Schedules I and II, Schedule III narcotics (opioid derivatives) and materials to manufacture gamma-hydroxybutyric acid, and select Schedule II and IV psychotropic agents.

Valid prescription requirements

The CSA provides special control mechanisms for licensed practitioners and pharmacists who dispense controlled substances in Schedules II to V to patients for legitimate medical purposes. Because controlled substances classified as Schedule I drugs are deemed to have no accepted medical purpose in the United States, they may only be used for research; they may not be dispensed to patients. Under the CSA, only licensed medical practitioners are authorized to prescribe to patients controlled substances listed in Schedules II to V. A prescription for a controlled substance must be issued for a legitimate medical purpose by an individual practitioner acting in the usual course of professional practice. Practitioners have a responsibility to ensure that the controlled substance is properly prescribed and dispensed, while pharmacists have corresponding responsibilities when dispensing the medication. In essence, the pharmacist is in the same position as the prescriber without having assessed the patient and must determine, by exercising professional judgment, if the prescription was issued in the usual course of treatment or for a legitimate purpose. Failure to establish legitimacy and knowingly filling a prescription that does not meet the intent of the law subjects the pharmacist to the same penalties as the prescriber. The law does not require a pharmacist to fill a prescription believed to be questionable or suspicious. Ways in which pharmacists can mitigate their corresponding responsibility is to validate the prescriber has a valid DEA number; use professional judgment, training, and experience; have a history with and knowledge of the patient; and have knowledge of and experience with the prescriber.

Prescription requirements

A valid prescription for a controlled substance must be dated and signed on the date it was issued. It must include the patient's full name and address and the practitioner's full name, address, and DEA registration number.

The prescription must also include the following:

- Drug name.
- Strength.
- Dosage form.
- Quantity prescribed.
- Directions for use.
- Number of refills authorized (if any).

A prescription must be written in ink or indelible pencil or be typewritten and must be manually signed by the practitioner on the date it was issued. The practitioner is responsible for ensuring the prescription conforms to all requirements of the law and regulations, both federal and state. Federally, there is no 90-day supply limit per prescription. However, insurance and state law may limit how many days of the supply may be dispensed, so the DEA allows prescribers to issue multiple prescriptions on the same day for Schedule II drugs. The prescriber must ensure the prescriptions are for a legitimate medical purpose and are not postdated, and the prescriber states on the face of the prescription the earliest date on which the prescription may be filled.

Electronic prescriptions

In June 2010, the DEA revised regulations giving authorized prescribers the option of issuing prescriptions for controlled substances electronically. The regulations permit pharmacies to receive, dispense, and archive electronic prescriptions. Pharmacies who choose to dispense controlled substances using electronic prescriptions must purchase an electronic pharmacy application that complies with all DEA requirements set forth in Part 1311 of Title 21 of the Code of Federal Regulations (Food and Drugs, 1973). Electronic prescriptions for controlled substances may be dispensed if the pharmacy has received an audit certification for its pharmacy application that allows digital signature, prescription archival, and ability to accept and store all DEA-required information; limits access to altering of the

electronic prescription; and provides an audit trail. Prescription records must be kept electronically and backed up daily. The prescriber must obtain authentication or digital signatures by a federally recognized private credential service provider, receive permission to access an electronic prescribing application with access controls, and sign the prescription using two-factor authentication. Computer-generated prescriptions that are printed or faxed from the prescriber to the pharmacy are not electronic prescriptions. States may also have local requirements regarding electronic prescriptions.

Schedule II

No controlled substance in Schedule II may be dispensed to a patient by a pharmacist without a written prescription from a practitioner, except in certain situations. The following situations are exempt from the written requirement and may be faxed:

- The prescription is for a Schedule II substance that is compounded for direct administration by the practitioner to a patient.
- The prescription is for a Schedule II medication for a resident of a long-term care facility.
- The patient is enrolled in hospice and the prescription notes that the patient is a hospice patient.

Partial filling of Schedule II substances is permitted if the full quantity is unavailable. The pharmacist has 72 hours to fill the remaining portion. If, after 72 hours, the remaining portion has not been filled, the pharmacist must notify the prescribing practitioner of the quantity dispensed.

In the case of an emergency, the practitioner may verbally authorize a pharmacist to fill a prescription for a Schedule II controlled substance. An emergency situation is defined as follows: immediate administration of the controlled substance is necessary for proper treatment of intended patient; no appropriate alternative treatment is available, including administration of a drug in Schedules III to V; and the prescribing practitioner is unable to provide a written prescription before the dispensing. Such an emergency authorization for a Schedule II substance may be filled by a pharmacist if the quantity of the drug prescribed and dispensed is limited to an amount adequate to treat the patient during the emergency period, usually 72 hours; the prescription is immediately reduced to writing by the pharmacist and contains all information required by federal regulations; the pharmacist makes a reasonable effort, in good faith, to determine the oral authorization came from a registered practitioner; and within 7 days after authorizing an emergency oral prescription, the prescribing individual practitioner must deliver a written prescription to the dispensing pharmacist and write "Authorization for Emergency Dispensing" and the date of the verbal order. The dispensing pharmacist must attach the paper prescription to the emergency prescription that had been reduced to writing. If the prescribing individual practitioner fails to deliver a written prescription, the pharmacist must notify the nearest DEA office. Failure of the pharmacist to comply with this requirement will void the authority to dispense without a written prescription of a prescribing individual practitioner.

Schedules III to V

Controlled substances in Schedules III to V may be dispensed by a pharmacist pursuant to either a written or an oral prescription, including a facsimile of a written prescription; these substances may be administered or dispensed directly by the practitioner in the course of professional practice without a prescription if allowed by state law. Practitioners are permitted to sign and transmit electronic prescriptions for controlled substances, assuming that the electronic prescription complies with detailed requirements set forth in the applicable federal regulations. A pharmacy may process electronic prescriptions for controlled substances if it has satisfied several conditions described in the applicable federal regulations. Prescriptions for controlled substances in Schedules III and IV may be filled or refilled by pharmacists up to five times within 6 months after the date the prescription was written. A pharmacist may partially dispense a prescription for Schedule III to V controlled substances provided that each partial filling is recorded in the same manner as a refilling, the total quantity dispensed in all partial fillings does not exceed the total quantity prescribed, and no dispensing occurs beyond 6 months from the date on which the prescription was issued.

A controlled substance that is a prescription drug may not be delivered, distributed, or dispensed by means of the Internet without a valid prescription. With respect to this provision of the CSA only, the term *valid prescription* means a prescription that is issued for a legitimate medical purpose in the usual course of professional practice by a practitioner who has conducted at least one medical evaluation of the patient in the physical presence of the practitioner.

Corrected or missing information

The pharmacist is authorized to make necessary changes to a valid controlled substance prescription in Schedules II to V. For Schedule II prescriptions, the pharmacist may add or change the patient's address. The pharmacist cannot change name of the patient, drug, or prescribing practitioner or the date of issuance. Changes in drug strength, dosage form, quantity, and directions for use may be accomplished provided that the pharmacist receives the information from the prescribing practitioner and receives verbal consent.

For Schedule III to V, the pharmacist may change the dosage form, drug strength, drug quantity, directions for use, or issue date only with the concurrence of the prescribing practitioner. Any changes should be noted on the prescription. Pharmacists and practitioners must comply with any state and local laws, regulations, or policies prohibiting any of these changes to controlled substance prescriptions.

The pharmacist is never permitted to make changes to the patient's name, the controlled substance prescribed, or the prescriber's signature.

Issuance of multiple prescriptions for schedule II controlled substances

The DEA allows individual practitioners to issue multiple prescriptions for Schedule II controlled substances on the same day, allowing the patient to receive up to a 90-day supply of a substance over a 90-day period. The prescriber must provide the patient with a separate complete prescription with directions for use and the date in which the prescription may be filled. Pharmacists may not fill the prescription before the written date. The law is clear in that the prescriber, acting in the usual course of practice, has determined that the patient has a legitimate medical need and that providing the 90-day supply does not create a situation of abuse or diversion.

Transferring controlled substance prescriptions

Transferring of a prescription for controlled substances listed in Schedules III to V between pharmacies is authorized on a one-time basis only if state law permits. For pharmacies that share a real-time, online database, the prescription may be transferred up to the maximum number of refills authorized by the prescriber provided that the system contains all required information of a valid controlled substance prescription.

Corresponding responsibility, red flags, and invalid prescriptions

The responsibility for proper prescribing and dispensing is shared between the practitioner who writes it and the pharmacist who fills it. If a pharmacist knowingly fills a prescription determined to be invalid, the pharmacist has violated the CSA and is subject to felony charges. The DEA has established a series of red flags to assist pharmacists in determining the legitimacy of controlled substance prescriptions. Red flags might include the following:

- The patient has traveled a significant distance to obtain the prescription.

- Prescriptions were issued by practitioners practicing outside their scope of practice.
- Patients pay with cash or credit card, instead of insurance.
- Prescriptions are for common cocktail medications (e.g., short-term pain relief).
- The prescriber's office is a significant distance from the pharmacy.

Case law judgments against pharmacies and pharmacists articulate the importance of resolving any red flags before dispensing or face legal implications. In addition to red flags, the pharmacist must practice due diligence in determining the legitimacy of a prescription before dispensing. Advancing technologies and cellular phone capabilities have created explicit opportunities for falsification of controlled substance prescriptions, placing increased burden on the pharmacist to exert due diligence before dispensing. Fraudulent prescriptions may include forgeries, photocopies, and the use of stolen prescription pads, a fictitious person or prescriber, an illegitimate medical purpose, altered quantities, and computer-generated phony prescription pads. Any questions concerning any aspect of a controlled substances prescription should be verified with the prescriber. If the patient is not known to the pharmacist, proper identification should be requested.

COMBATING METHAMPHETAMINE

Concerns over the manufacturing of methamphetamine resulted in the Comprehensive Methamphetamine Act of 1996, the Methamphetamine Anti-Proliferation Act of 2000, the Combat Methamphetamine Epidemic Act of 2005, and the Methamphetamine Production Prevention Act of 2008. The 1996 and 2000 laws included increased penalties for trafficking and manufacture of methamphetamine and placed requirements on registration, recordkeeping, and reporting on sales of ephedrine, pseudoephedrine, and phenylpropanolamine. The Combat Methamphetamine Epidemic Act was enacted in 2006 to control the sale of all single- and multi-ingredient pseudoephedrine- and ephedrine-containing products used in the manufacturing of methamphetamine. This law placed nonprescription ephedrine, pseudoephedrine, and phenylpropanolamine in the new CSA category of "scheduled listed chemical products" and required strict sales restrictions, storage requirements, and recordkeeping requirements. Specifically, the law requires these products to be placed behind a counter or, if on the floor, in a locked cabinet; sets sales limits of 3.6 g/day of base product or 9 g/30-day base product; requires all product to be in a blister package; and requires documentation in a logbook. The 2008 act established a real-time electronic logging system with signature capture. Training for requirements rests with the employer, who must certify employees understand the law. The employer is responsible for maintaining employee training records, enforcing sales limits, ensuring products are stored in accordance with the law, and ensuring all sales are documented appropriately.

ANABOLIC STEROIDS CONTROL ACT OF 1990

The Anabolic Steroids Control Act of 1990 moved this class of medications from noncontrolled into controlled Schedule III of the CSA. Historically, anabolic steroids, which include testosterone, androstenedione, nandrolone, and methandrostenolone, have been used to enhance athletic ability and endurance in athletes and bodybuilders. These agents improve performance by making muscle cells larger and by allowing the body to recover more quickly from the stress of exercise. Anabolic steroid use is no longer limited to bodybuilders and professional athletes, further prompting the need to reclassify them as controlled substances.

DESIGNER ANABOLIC STEROID CONTROL ACT OF 2014

The Designer Anabolic Steroid Control Act of 2014 addressed the modification of a dietary supplement with the chemical cousins of anabolic steroids as a means of circumventing the list of controlled substances. It calls for the classification of these agents, purposefully created to produce the pharmacological effects of testosterone or promoted as causing an effect similar to testosterone, as Schedule III controlled substances.

CONCLUSION

The Controlled Substance Act continues to evolve and provide guidance in response to current threats to the health and safety of the public. The opioid crisis has prompted a renewed emphasis on the importance of corresponding responsibility, attentiveness to potential red flags, and access to controlled substances. Changes within the scheduling of controlled substances, driven by prevalence of misuse and abuse, have affected the practice of pharmacy directly. Increased recordkeeping, heightened storage requirements, and ready access to inventory affect daily workload, workflow, and ultimately patient care.

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Avariety of federal laws that affect pharmacists and pharmacy practice go beyond the Federal Food, Drug, and Cosmetic Act (FDCA) and the federal Controlled Substances Act. This chapter addresses other federal legislation that has affected the practice of pharmacy and medication distribution. Current standards in patient counseling, while different in each state, are part of federal legislation that was previously focused on finance and not necessarily patient care (U.S. Food and Drug Administration [FDA], 2017). The security and privacy of patient information, with advances in technology, created requirements for pharmacies when disposing of and discussing personal health information and safeguards associated with transmitting patient information telephonically or electronically. The FDA-driven interchangeability of biologics under similar guidance as generic substitution, creating The Purple Book of biosimilars, is discussed, as well as the law governing the use of naloxone by first responders (FDA, 2017).

POISON PREVENTION PACKAGING ACT OF 1970

The Poison Prevention Packaging Act of 1970 (PPPA), under the jurisdiction of the FDA until 1973, is now administered by the U.S. Consumer Product and Safety Commission (CPSC). The PPPA gives the CPSC the authority to require special packaging of household products and drugs to protect children from serious injury or illness (PPPA, 1970). Before the PPPA, poisonings by common household substances, including medicines, had long been considered by pediatricians to be the leading cause of injuries among children under 5 years of age. After the PPPA and the implementation of standards to prevent poisonings, the CPSC reported that child-resistant packaging reduced the oral prescription medicine-related death rate by up to 1.4 deaths per million children under the age of 5 years. This represented a reduction in the rate of fatalities of up to 45% from levels that would have been projected in the absence of child-resistant packaging requirements and equated to about 24 fewer child deaths annually (CPSC, 2005).

The purpose of the PPPA was to give to the CPSC authority to require special packaging of household products and drugs to protect children from serious injury or illness. Manufacturers are required to perform tests to ensure that children under 5 years of age would find the packaging significantly difficult to open. In these tests, pairs of children aged 42 to 51 months are selected and given 5 minutes in which to open the packages. If the children cannot open the package, they are then given a visual demonstration and another 5 minutes in which to open the package. The package is considered child resistant if not more than 20% of the 200 children tested can open the package. Adults are also tested with the same packages. Adults are likewise given a 5-minute period to open and properly close the package. If 90% of the 100 adults tested can open and close the child-resistant package, it passes.

The PPPA affects pharmacy practice and manufacturing of over-the-counter (OTC) and prescription medications in many ways. Failure to comply with packaging requirements or any applicable regulations is considered a misbranding violation under the FDCA. A pharmacist could be prosecuted and imprisoned for not more than 1 year or sentenced to pay a fine of not more than $1,000, or both.

All legend drugs and controlled dangerous substances must be packaged in a child-resistant container, with limited exceptions. Pharmacists should be familiar with their responsibilities under the PPPA. OTC products also require child-resistant packaging, with one exception: Manufacturers may market one size of an OTC product for the elderly or handicapped in noncompliant containers provided that the package states, "This package for households without young children."

The pharmacist must dispense oral prescription drugs in special packaging unless the patient or prescribing practitioner requests nonspecial packaging or the drug is exempted (PPPA, 1970).

Patient or prescriber request exemptions to the PPPA include the following:

- Requested non-child resistant containers.
- Blanket requests made by the patient only.
- No written requirement or document request.
- Pharmacist initiated request for the patient's decision.

Special packaging is required for all prescription medications except the following:

- Sublingual nitroglycerin tablets.
- Erythromycin ethyl succinate granules containing not more than (NMT) 8 g.
- Erythromycin ethyl succinate tablets containing NMT 16 g.
- Anhydrous cholestyramine or colestipol powder.
- Potassium supplements in unit dose forms with NMT 50 mEq.
- Sodium fluoride preparations with NMT 264 mg.
- Mebendazole.
- Methylprednisolone in packages with NMT 84 mg.
- Pancrelipase.
- Oral contraceptives, conjugated estrogens, norethindrone acetate, and hormone replacement.
- Therapy products in memory-aid dispensers, including prednisone in packages with NMT 105 mg and sucrose products.

Other exemptions to the PPPA include the following:

- Bulk containers not intended for household use.
- Drugs distributed to patients (e.g., hospital or nursing home).
- Package size designed for and labeled as "for households without young children".

In addition to most prescription medications, except those listed earlier, the following substances require special packaging:

- Aspirin-containing products.
- Oil of wintergreen if more than 5% by weight of methyl salicylate.
- Controlled medications.
- Methanol.
- Iron-containing medications.
- Dietary supplements with iron.
- Acetaminophen (except effervescent tablets or granules).
- Diphenhydramine with NMT 66 mg.
- Ibuprofen.
- Loperamide.
- Lidocaine.
- Dibucaine.
- Naproxen.
- Ketoprofen.
- Fluoride.
- Minoxidil.
- Imidazolines found in ophthalmic and nasal products.
- Any drug switched from prescription to OTC status.

PRESCRIPTION DRUG MARKETING ACT OF 1987

The Prescription Drug Marketing Act of 1987 (PDMA) amended the FDCA to ensure drug products purchased by consumers are safe and effective and to reduce the potential public health risks that may result from diversion of prescription drugs from legitimate drug distribution systems. The PDMA expressly prohibits the introduction or sale of counterfeit, adulterated, misbranded, ineffective, subpotent, or expired drugs from distribution in the United States and the reimportation of any drug that is not imported by the original manufacturer. The intent is to strengthen the chain of custody for all drug products and establish strict accountability in an effort to prevent drug diversion. The act sought to curtail lack of accountability, which resulted in a multimillion-dollar submarket of diverted sample and discounted drugs to secondary markets. The PDMA set processes and procedures for how drug samples are distributed; bans the sale, trade, or purchase of samples; mandates the storage, handling, and recordkeeping of drug samples; and prohibits resale. In accordance with the law, drug samples may only be distributed to practitioners licensed to prescribe upon written request that includes the practitioner's name, address, and professional designation; the identity and quantity of the drug sample requested; the manufacturer; and the practitioner's signature. The act mandated the appropriate storage of drug samples to ensure the stability, integrity, and effectiveness of the drug and assurances that the samples are free from contamination, degradation, and adulteration. Before the act, samples could be secured in non-temperature-controlled storage locations. The act also required an annual inventory of all drug samples in the possession of pharmaceutical sales representatives and mandated reporting of any significant loss or discrepancy.

OMNIBUS BUDGET RECONCILIATION ACT OF 1990

The Omnibus Budget Reconciliation Act of 1990 (OBRA-90) changed the face of pharmacy by placing expectations on the pharmacist to not just provide product dispensing but also engage in a higher level of service, that of pharmaceutical care. The goal of pharmaceutical care is to elevate the practice of pharmacy to take ownership in improving the overall health care of patients. As a result, OBRA-90 mandated changes in how pharmacists interact with their patients. While the primary goal of OBRA-90 was to save the federal government money by improving therapeutic outcomes, the method to achieve these savings was implemented by requiring the pharmacist to counsel patients, conduct prospective drug utilization review (ProDUR), and adhere to recordkeeping mandates. The focus of OBRA-90 was directed at the Medicaid program. Specifically, ProDUR language requires state Medicaid provider pharmacists to review Medicaid recipients' entire drug profile before filling their prescriptions. The intent of ProDUR is for the pharmacist to conduct a complete evaluation of a patient's medication history to detect potential drug therapy problems before dispensing in an effort to resolve any issues before the patient takes the medication. The advent of clinical decision support-based computer programs has advanced the pharmacists' ability to identify potential problems and address them before dispensing. How issues or concerns are addressed is up to the pharmacists' professional judgment, which could include contacting the prescriber or refusing to fill the medication. In conducting ProDUR, the pharmacist must screen for the following:

- Therapeutic duplications.
- Drug-disease contraindications.
- Drug-drug interactions.
- Incorrect drug dosage.
- Incorrect duration of treatment.
- Drug-allergy interactions.
- Clinical abuse or misuse of medication.

OBRA-90 also required states to establish standards regarding patient counseling. Specifically, pharmacists must make the offer to discuss drug therapy with patients or caregivers when filling prescriptions for them. Counseling discussions must address any significant concerns the pharmacist has regarding medication therapy.

The pharmacist, at a minimum, should discuss the following:

- Name and description of the medication.
- Route of administration.
- Dose and dosage form.
- Duration of therapy.
- Special directions and precautions for preparation, administration, and use by the patient.
- Common and serious side effects.
- Self-monitoring techniques of drug therapy.
- Proper storage.
- Refill information.
- Appropriate action in the case of a missed dose.

Under OBRA-90, Medicaid pharmacy providers must maintain accurate Medicaid patient records that include the following:

- Patient's demographics (name, age, and gender).
- Patient's general information (address and phone number).
- Patient's history (disease states, known allergies, and drug reactions).
- Comprehensive list of medications and relevant devices.
- Pharmacist's comments about the patient's drug therapy.

Although OBRA-90 was geared toward Medicaid patients, because the federal government cannot regulate professional practice, the overall result of the legislation is that the same type of care is rendered to all patients, not just Medicaid patients. States did not want one standard of pharmaceutical care for Medicaid patients and one for non-Medicaid patients, so in the end, all patients fall under the same mandate for pharmaceutical care requiring ProDUR, patient counseling, and appropriate documentation. OBRA-90 also addressed the issue of restrictive formularies among state Medicaid programs. Because the restrictive nature resulted in the denial of important medications to the poor, OBRA-90 disallowed restrictive formularies in Medicaid programs.

OMNIBUS BUDGET RECONCILIATION ACT OF 1993

The significance to pharmacy practice of the Omnibus Budget Reconciliation Act of 1993 (OBRA-93) was the reversal of OBRA-90 language that disallowed restrictive formularies for state Medicaid programs. OBRA-93 allowed states to establish formularies for Medicaid programs and included a provision that coverage of new drugs approved by the FDA require prior authorization for the first 6 months following approval. The act also allowed drugs to be excluded from formulary only if the drug does not have a significant, meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcomes over other drugs included in the formulary (Ghasemi & Kavarian, 2015). OBRA-93 places decision making regarding medications on pharmacy and therapeutics committees, which evaluate drugs based upon evidence and make determinations on coverage based on cost effectiveness. The act discusses three types of formularies: open formularies for which any prescribed prescription drugs are covered; preferred formularies that allow access to preferential drugs for a reduced copayment – that is, brand versus generic; and closed formularies for which any drug that is not on the formulary will not be provided. Considering the pros and cons of formularies, restricting medication availability can reduce patients' out-of-pocket costs and encourage prescribers to use the most clinically effective medication in a therapeutic class. On the negative side, formularies can create issues with lapses in communication among health plans, pharmacy benefits managers, and patients, and coverage decisions may be influenced by pharmacy benefits manager reimbursements (Ghasemi & Kavarian, 2015).

HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT OF 1996

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) is the most significant piece of federal legislation to affect pharmacy practice since OBRA-90. HIPAA was crafted originally with the intent to better protect health insurance coverage for employees and their families when employees changed employers or became uninsured (i.e., to ensure portability of health insurance). The HIPAA provisions that cover data privacy, data security, and data breach notification have the greatest impact for pharmacy practice by requiring privacy of patient information, standardizing electronic healthcare transactions for any data stored or transmitted electronically, and creating a duty to notify the patient should a breach occur. Violations of HIPAA may result in civil fines from $100 for a single violation to $1.5 million for identical violations in a calendar year.

Privacy provisions

The HIPAA Privacy Rule is designed to safeguard the privacy of protected health information (PHI). PHI is individually identifiable health information that includes demographic information (gender, race, and age); details specific to the patient's physical and mental health or medical condition, such as diagnosis or diagnosis codes and the provision of health care to the individual; past, present, or future payment for providing health care to the patient; and information that identifies the patient or that can be used to identify the individual. PHI includes many common identifiers, such as name, address, date of birth, and Social Security Number alone or in combination when they can be associated with the specific health information. A patient's medical record, laboratory report, or prescription label is PHI because the documents contain the patient's name and other identifying information associated with the patient, as does a piece of paper with the date of birth and phone number of the patient. Aggregate information is not considered PHI because patient-specific information is not included. Much discussion has occurred over using electronic patient boards to display names when prescriptions are ready. As it stands, identifying information alone – personal name, address, or phone number – is not enough to be considered PHI, because the information does not include or cannot be associated with health-related data, such as medication and medical condition. Pharmacies that maintain patient information or conduct financial and administrative transactions electronically, such as billing and fund transfers, must comply with HIPAA. While HIPAA places stringent requirements on pharmacies to adopt policies and procedures relating to the protection of patient PHI, the law gives patients the right to access their information, the right to seek details of the disclosure of information, and the right to view the pharmacy's policies and procedures regarding confidential information.

From the pharmacy practice perspective, most records kept in the pharmacy meet the definition of PHI, including prescription records, billing records, patient profiles, and counseling records. As such, HIPAA requires pharmacists to implement policies and procedures for addressing the use, disclosure, and request for PHI. Pharmacies must post their entire notice of privacy practices in a clear and prominent location, as well as in any electronic format, such as on a website. HIPAA requires patients to be informed of the privacy practices of the pharmacy and notified of these rights and practices. The pharmacy must appoint a compliance or privacy officer to work with personnel in assessing operations, identifying areas that need to be addressed, and ensuring compliance with HIPAA. All pharmacy employees, including pharmacists, technicians, and any other individuals who assist in the pharmacy, must be trained on the requirements. Finally, in some situations, it is necessary for the pharmacy to allow disclosure of PHI to a person or organization defined in HIPAA as a business associate. Business associates perform a function that requires disclosure of PHI, such as billing services, claims processing, utilization review, or data analysis. Examples of business associates that may interface with pharmacy include third-party administrators of health, a consultant performing utilization reviews, and a pharmacy benefits manager that is responsible for a health plan's pharmacy network. Under HIPAA, a pharmacy is allowed to disclose PHI to a business associate if the pharmacy obtains satisfactory assurances that the business associate will use the information only for the purposes for which it was engaged by the pharmacy.

The HIPAA privacy standards allow pharmacies and other health providers to use and disclose PHI, without authorization from the patient or the patient's personal representative, for purposes of treatment, payment, and healthcare operations. The pharmacy must employ reasonable safeguards to protect the privacy of patient information, which might include using a secured network for refill requests or locating the fax machine in a secure place in the pharmacy to prevent unauthorized access to faxes.

Security provisions

The HIPAA security provisions went into effect April 20, 2005, almost 2 years after the privacy provisions. These security standards establish the requirements to safeguard and protect the confidentiality of PHI that may be threatened by unauthorized access and interception during electronic transmission. Like the privacy provisions, any pharmacy that transmits or receives any health information in electronic form is required to comply with the security rules. The standards define administrative, physical, and technical safeguards that the pharmacist must consider to protect the confidentiality, integrity, and availability of PHI. The security requirements specifically state that the entity, in this case, the pharmacy, must protect against any reasonably anticipated threats, uses, or disclosures of PHI. Safeguards could include shredding waste, using privacy filters on computer screens visible to customers, limiting the number of employees who have full access to patient records, encrypting computer files that contain PHI, and using a secure e-prescribing network to receive new prescriptions or request

and receive refill authorizations. The expansion of the use of the technology has advanced potential risks of hackers, transmission of data over an open network, encryption software failure, use of wireless networks, and loss of portable devices. The security rules allow healthcare facilities and entities the flexibility to determine which security measures best serve their operation and emphasize risk analysis in deciding the most viable solution. As an example, while shredding of PHI-containing documents is an option, HIPAA does not require specific measures, just that they be reasonable and appropriate in guarding information.

A unique aspect of the security provisions is that they include both required and addressable implementation specifications. Required implementation specifications are those that must be met, whereas in addressable specifications, the pharmacy can decide whether the suggested safeguards are reasonable and appropriate given the size and capability of the organization, as well as the risk. Cost is a consideration when determining whether to implement a particular specification; however, a clear requirement exists that adequate security measures will be implemented.

Breach notification

Effective September 2009, pharmacies and other healthcare companies must notify patients if there is a breach of PHI privacy. Notification is only required when PHI is unsecured. Unsecured PHI is when information is in a form that could be read, used, deciphered, or accessed by unauthorized individuals. Examples of unsecured PHI include whole pieces of paper, torn pieces of paper with patient information that can be pieced together, and unencrypted files with patient information such as in email or on hard drive, flash drive, or CD. In all circumstances, the pharmacy must notify patients in writing within 60 days if their information has been breached. The notification must include the type of breach and a list of information involved. An example might be disposing of a patient's old prescription bottles in the trash or throwing out an edited label. If the breach affects 500 or more patients, the media must be notified, along with the secretary of the U.S. Department of Health and Human Services (HHS). Each pharmacy must keep a record of all breaches, which must be reported to the HHS annually by March 1.

HIPAA in practice

In pharmacy practice, it is the duty of the pharmacist and pharmacy staff to protect the privacy of patients. Violating a patient's privacy includes improper disclosure of PHI, unauthorized access to confidential health information, discussing patient-specific information within earshot of other patients, and in some case sharing information with a patient's family. The pieces of PHI are what make a patient identifiable. As an example, if a pharmacist writes a patient's name, date of birth, and phone number on a piece of paper, it should be shredded or destroyed. When answering the telephone and responding to patient questions, care should be taken to ensure other patients cannot overhear the conversation. Advising a patient that a prescription is ready is different from telling the patient that a medication for a transmitted disease is ready. Likewise, having a conversation outside of the pharmacy, such as in an elevator or coffee shop, and discussing a specific patient's situation where others can hear could be a violation. When sending a refill request or prescription clarification to a prescriber's office, reasonable safeguards must be in place to protect the privacy of the patient. Confirming the fax number, requesting refills using a secure e-prescribing network, or using the fax machine within the physical security of the pharmacy are reasonable methods of securing patient-specific information. Some pharmacies use their patient profile record not only to document allergies and special requests but also to note patient-specific comments. Under HIPAA, patients have the right to request access to their PHI, so it is a good idea to avoid entering negative and unprofessional comments in a patient's profile. Patients also have the right to limit pharmacy disclosure of their PHI and request the pharmacy communicate with them directly and confidentially. A common situation is when a family member comes to the pharmacy to pick up their prescriptions and is offered medication for another family member without authorization or disclosure. In recent years, the mother has been asked whether she wants to pick up her daughter's birth control pills, and a husband discovered his wife has been on birth control when he thought they were trying to have a child. The diligence applies when leaving messages regarding medication specifics. In practice, pharmacy personnel must be mindful, use good judgment, and be cautious of what they share and with whom.

HEALTH INFORMATION TECHNOLOGY FOR ECONOMIC AND CLINICAL HEALTH ACT OF 2009

With the expected growth of advancing technologies, the Health Information Technology for Economic and Clinical Health Act of 2009 (HITECH) focused attention on the need to widen the scope of privacy and security protections covered in HIPAA, calling for more enforcement and legal liability for noncompliance. Specifically, HITECH focused on heightening the privacy and security of electronic patient information and prescription data. The act contains language that implies that a historic lack of full enforcement, and under HITECH, civil penalties for willful neglect are increased. These penalties can extend to $250,000, with penalties for repeat or uncorrected violations extending to $1.5 million. Under certain conditions, HIPAA's civil and criminal penalties extend to business associates. Like HIPAA, HITECH does not allow an individual to bring action against a provider; however, it does allow a state attorney general to bring an action on behalf of residents. In addition, the HHS must conduct periodic audits of covered entities and business associates. The legislative intent is to provide "enhanced enforcement" (HHS, 2017).

HITECH established data breach notification requirements for unauthorized uses and disclosures of unsecured PHI. Unsecured PHI is defined as information that is not rendered unusable, unreadable, or indecipherable to unauthorized people. Requirements are similar to breach laws related to personally identifiable financial information (e.g., banking and credit card data). The act requires that patients be notified of any unsecured breach. If a breach affects 500 patients or more, then the HHS must also be notified so that it can post the breaching entity's name on the HHS website; major media outlets will also need to be notified. Notification of a breach is triggered whether the unsecured breach occurred externally or internally.

With regard to electronic health records (EHR), the act requires covered entities to implement an audit trail accounting for all disclosures and access of information. The act also gives patients the right to obtain, upon request, their PHI electronically from a provider who has implemented an EHR program. Pharmacies with electronic records and prescription data collection fall under this provision and must provide electronic copies of requested information upon request of the patient. Overall, HITECH is used to enforce security standards of HIPAA and compliance surveillance.

BIOLOGICS PRICE COMPETITION AND INNOVATIVE ACT OF 2009

The Biologics Price Competition and Innovative Act of 2009 (BPCI Act), part of the Affordable Care Act, is similar in concept to the Drug Price Competition and Patent Term Restoration Act of 1984 (commonly known as the Hatch-Waxman Act) in that it created expedited processes for the approval of drug products. The BPCI Act follows prior FDA guidance that allows manufacturers to show bioequivalency to a pioneer product without duplicating testing. In terms of biologics, a manufacturer may seek biosimilarity, which means "that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and "there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity and potency of the product" (BPCI Act, 2009). For a biologic to be considered interchangeable, the product must be shown to be biosimilar to the reference product and will produce the same clinical results. Simply put, the products are not required to be identical, just interchangeable. For a product to be deemed interchangeable, it must be administered more than once to a patient without decreased efficacy or safety from the reference product. Interchangeable products may be substituted for the reference product by a pharmacist without the intervention of the prescribing healthcare provider. Pharmacists should refer to state law and insurance coverage on the requirements for prescribers to mandate brand name. A complete list of biological products, including those deemed biosimilar and interchangeable, can be found in the Purple Book. The Purple Book includes the date a biological product was licensed and whether FDA evaluated the biological product for reference product exclusivity. The first biosimilar product approved in the United States was Zarxio (filgrastim) by Sandoz. Zarxio is interchangeable with Neupogen.

COMPREHENSIVE ADDICTION AND RECOVERY ACT OF 2016

The Comprehensive Addiction and Recovery Act of 2016 (CARA, Public Law 114-198) was enacted with the intent of coordinating a collaborative response to addiction, which includes prevention, treatment, recovery, law enforcement, criminal justice reform, and overdose reversal (Community Anti-Drug Coalitions of America, n.d.). CARA focused on expanding prevention and educational efforts – particularly aimed at teens, parents and other caretakers, and aging populations – to prevent the abuse of methamphetamine, opioids, and heroin and to promote treatment and recovery. The act expanded the availability of naloxone to law enforcement agencies and other first responders to help in the reversal of overdoses to save lives. It also expanded resources for identifying and treating individuals suffering from addiction disorders who are incarcerated, calling for collaboration and the provision of evidence-based treatment. CARA addressed the issue of disposal of unwanted prescription medications to keep them out of the hands of children and adolescents through the establishment of takeback programs and registered collectors. To address the opioid crisis, CARA mandated the launch of evidence-based opioid and heroin treatment and intervention programs to expand best practices throughout the country and a medication assisted treatment and intervention demonstration program. CARA also called for strengthening prescription drug monitoring programs through grant funding to help states monitor and track prescription drug diversion and to help at-risk individuals access services. Specifically, CARA established opioid overdose reversal medication access and education grant programs, creating grants to encourage pharmacies to implement strategies to dispense opioid overdose reversal drugs pursuant to a standing order; develop and provide training on how to administer opioid overdose reversal drugs and devices; and educate the public concerning the availability of overdose reversal drugs or devices.

CONCLUSION

This chapter discussed several federal laws that affect how pharmacists practice every day. While the Poison Prevention Packaging Act initially focused on household poisons and how to prevent poisonings, expanding the need for child-safe packaging to over-the-counter medications and prescription drugs has significantly decreased the incidence of childhood poisoning. The implications of the Prescription Drug Marketing Act and the proper use, storage, and accountability of pharmaceutical samples are intended to prevent sale and diversion of these items to secondary markets. The Omnibus Reconciliation Act of 1990 expanded the role of the pharmacist by mandating prospective review of patient medication profiles, identification of medication-related issues, intervention as necessary with prescribers, and provision of counseling to patients on appropriate use. Health Insurance Portability and Accountability Act called for the safeguarding of personal health information, with provisions for security and privacy of patient-specific health information. The Health Information Technology for Economic and Clinical Health Act of 2009 set forth stiffer penalties and responsibility to notify patients of a data breach of unsecured PHI and the HHS of a breach of 500 or more. The Biologics Pricing Act mirrored the Hatch-Waxman Act by adopting a similar process in determining interchangeability of biological agents as biosimilar. The chapter concluded with a brief discussion of Comprehensive Addiction Recovery Act which calls for collaboration in addressing the opioid addiction crisis and established protocols for the use of naloxone without a standing order by first responders and pharmacists.

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Final Examination Questions

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61. The Food and Drug Administration (FDA) was created by the:
    a. Durham-Humphrey Amendment of 1951 (DHA).
    b. Harrison Narcotics Act of 1914.
    c. Kefauver-Harris Amendments of 1962.
    d. Federal Food and Drug Act of 1906.

62. The Pure Food and Drug Act prohibits the:
    a. Manufacturing of cosmetics.
    b. Interstate sale of adulterated drugs.
    c. International marketing of food and drugs.
    d. Development of manufacturing and branding standards.

63. A drug is adulterated if:
    a. Labeling is false or misleading.
    b. It has been prepared under sanitary conditions.
    c. Its strength differs from the product it represents.
    d. The manufacturer is not registered with the FDA.

64. If a pharmacist fills a prescription that is not labeled with the generic name of the medication, this is an example of:
    a. Misbranding.
    b. Misleading.
    c. Adulteration.
    d. Corruption.

65. Which of the following amendments to the Federal Food, Drug, and Cosmetic Act created two classes of medications: prescription and nonprescription?
    a. DHA.
    b. Harrison Narcotics Act.
    c. Kefauver-Harris Amendments.
    d. Omnibus Budget Reconciliation Act.

66. The Medical Device Amendments of 1976 required:
    a. Devices to undergo premarket testing.
    b. Conformation with state guidelines.
    c. Payment of a $2.5 million penalty by the Dalkon Shield manufacturer.
    d. Expedited approval for drugs to treat rare conditions.

67. The Orphan Drug Act of 1983 provides manufacturers with incentives to develop and market drugs for rare diseases or conditions that:
    a. Affect fewer than 100,000 Americans.
    b. Have an unmet medical need.
    c. Lead to terminal illnesses.
    d. Lead to illnesses requiring emergent treatment.

68. The Hatch-Waxman Act provided generic manufacturers with certain incentives. Which of the following BEST describes one of these incentives?
    a. 200 days of exclusivity.
    b. Allowing testing for bioequivalence to occur after the branded product patent had expired.
    c. Required the filing of a new drug application for market approval.
    d. 180 days of exclusivity for the first manufacturer to have an abbreviated new drug application approved.

69. Which legislative act provided for the expedited study and approval of fast-track drugs?
    a. Kefauver-Harris Amendments.
    b. Drug Price Competition and Patent Term Restoration Act.
    c. Food and Drug Administration Modernization Act.
    d. Prescription Drug Marketing Act.

70. The amendment that provided the FDA with the authority to inspect compounders on a risk-based schedule was the:
    a. Compound Quality Act.
    b. Drug Quality and Security Act.
    c. Food and Drug Administration Modernization Act.
    d. Food and Drug Administration Amendments Act.

71. A Schedule II controlled substance is defined by the Controlled Substances Act (CSA) as:
    a. A drug or other substance that has a low potential for abuse.
    b. A drug or other substance that has a no accepted medical use in treatment in the United States.
    c. A drug or other that may lead to severe psychological or physical dependence.
    d. A drug that has no accepted safety for use under medical supervision.

72. Medical marijuana has been decriminalized in 29 states and in Washington, DC. While the state laws are in direct defiance of federal law, the attorney general's office identified eight enforcement priorities regarding marijuana use. Which of the following represents one of the priorities?
    a. Preventing the remaining 21 states from legalizing marijuana.
    b. Preventing drugged driving and other adverse public health consequences associated with marijuana use.
    c. Preventing marijuana growers from profiting from the sales.
    d. Allowing cartels to profit from medical marijuana sales.

73. Which Drug Enforcement Administration (DEA) form is used by pharmacists to report theft or significant loss?
    a. DEA Form 222.
    b. DEA Form 41.
    c. DEA Form 224.
    d. DEA Form 106.

74. When ordering Schedule II drugs via DEA Form 222, which of the triplicate form or forms is or are sent to the supplier?
    a. Copy 1.
    b. Copy 2.
    c. Copy 3.
    d. Copies 1 and 2.

75. When partially filling a Schedule IV prescription, which of the following is required?
    a. No dispensing occurs after 12 months following the date on which the prescription was issued.
    b. Each partial filling is recorded in the same manner as a refilling.
    c. Schedule IV prescriptions may not be partially filled.
    d. Only a written prescription may be partially filled.

76. Which information on a Schedule II prescription may be modified by the pharmacist?
    a. The pharmacist may change the name of the prescriber.
    b. The pharmacist may adjust the date of issuance.
    c. The pharmacist may add or modify the address of the patient.
    d. The pharmacist cannot legally modify any part of the prescription.

77. How many times, in accordance with federal law, may a prescription for a Schedule III controlled substance be transferred to another pharmacy if the pharmacies online database is not shared?
    a. Never.
    b. Once.
    c. Twice.
    d. Three times.

78. A pharmacist who knowingly fills a prescription deemed to be invalid has violated the CSA and can be charged with which of the following?
    a. A class A misdemeanor.
    b. A class B misdemeanor.
    c. A felony.
    d. A pharmacist cannot be legally charged.

79. Red flags are key indicators that a controlled substance prescription may not be legitimate or valid. An example of a red flag is:
    a. A patient who uses prescription drug coverage or insurance for the medication.
    b. A patient has traveled a significant distance to obtain the prescription.
    c. A prescription prescribed by a practitioner practicing within the scope of his or her practice.
    d. A prescriber's office that is across town from your pharmacy.

80. Under the Combat Methamphetamine Epidemic Act, the seller is required to maintain storage of medications in the scheduled listed chemical products:
    a. On the shelf in front of the pharmacy.
    b. Behind the counter.
    c. In an automated dispensing cabinet.
    d. Wherever convenient; there are no restrictions for storage, only for purchases.

81. In an effort to protect children from accidental poisonings with household substances, Congress enacted:
    a. Packaging guidance for all hazardous substances.
    b. Packaging guidance for medications.
    c. The Poison Prevention Packaging Act.
    d. The Prescription Drug Marketing Act.

82. Medications and prescription drugs that are dispensed directly to the patient are required to be in child-resistant containers. Which of the following medications are exempt from this requirement?
    a. Any medication in a unit dose form.
    b. Any potassium supplements in unit dose forms.
    c. Methylprednisolone tables with no more than 84 mg of drug per package.
    d. Aspirin-containing products.

83. Karen is the new pharmacist at an independent chain pharmacy. She had recently ordered a supply of pregabalin in various strengths to support a new pain management physician practicing in town. For some reason, the order did not get processed, and the store is running low on stock before a long holiday weekend. Karen contacts the owner who advises her not to worry; he will take care of it. Shortly thereafter, the owner arrives with a significant supply. Karen begins to process the patient orders and sees on the bottles "professional sample – not for sale." Which federal law addresses the legality of this practice?
    a. Sherman antitrust law.
    b. Prescription Drug Marketing Act.
    c. Food, Drug, and Cosmetic Act.
    d. Code of Federal Regulations.

84. The Prescription Drug Marketing Act mandates that:
    a. Prescription drugs be fairly marketed.
    b. Drug samples be stored properly.
    c. Drug samples be fairly distributed.
    d. Drug samples that are resold be properly labeled.

85. Joe is the staff pharmacist at a local chain drugstore. His regional director sent out a memo discussing the chain's recent issues with noncompliance with the Omnibus Budget Reconciliation Act of 1990 (OBRA-90) counseling requirements. Several pharmacists had been fined for not providing counsel upon dispensing. Joe is a recent graduate and does not want to jeopardize his license or provide substandard patient care. What direction should Joe give to his staff?
    a. Be sure to provide every patient with drug information.
    b. Be sure to offer counseling by the pharmacist to every patient.
    c. Identify to him any Medicaid patients, and he will talk to them personally.
    d. Offer to counsel but tell patients that during peak times, talking with the pharmacist may require a 20-minute wait.

86. Under OBRA-90, a pharmacist must conduct a medication review that includes which of the following?
    a. Comparison of the patient's treatment to disease state guidelines.
    b. A pharmacoeconomic analysis of the patient's treatment.
    c. Screen for drug-drug interactions.
    d. Review of drug formulary status.

87. Under the Health Insurance Portability and Accountability Act (HIPPA), which of the following is considered protected health information (PHI)?
    a. Aggregate information on a group of patients with diabetes.
    b. The patient's diagnosis.
    c. The patient's last name on an electronic board in a pharmacy.
    d. A patient's phone number.

88. Under HIPPA, a pharmacy is allowed to disclose PHI to a business associate in which of the following situations?
    a. The pharmacy is never allowed to disclose PHI to a business associate.
    b. If the pharmacy obtains assurance that the business associate will only use the PHI for purposes for which it was engaged by the pharmacy.
    c. If the business associate is also a family member.
    d. If the business associate is the patient's employer.

89. John is the pharmacist in training at Valley Pharmacy. It's an incredibly busy day, and John notices that old prescription labels, patient information, and other patient-specific information are being disposed of with the regular trash. Before asking questions, John looks for the pharmacy policy on disposal of PHI and cannot find guidance. John asks the lead technician, Sara, about the practice. Sara advises John not to worry – all trash goes to the dumpster and is incinerated every other day. John is concerned that this practice does not comply with HIPAA. Should John be concerned?
    a. No, the law does not specify how an entity might dispose of PHI.
    b. No concern necessary – so long as the information is incinerated.
    c. Yes. This practice allows access to PHI in the dumpster until it is incinerated.
    d. Yes. HIPPA mandates pharmacies that hire a business to dispose of PHI.

90. Which of the following references serves as a resource of biological products deemed biosimilar and interchangeable?
    a. Purple Book.
    b. Orange Book.
    c. Black Book.
    d. Yellow Book.

Chapter 6: The Role of the Pharmacist in the Opioid Crisis

5 Contact Hours

By: Laura Palombi, PharmD, MPH, MAT

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Learning objectives

After completing this course, the learner will be able to:

- Describe the historical context of the opioid crisis, including trends in substance use globally and in the United States, as well as contributing factors to the opioid crisis in both health care and the community.
- Describe key components of the Centers for Disease Control and Prevention (CDC) *Guidelines for Prescribing Opioids for Chronic Pain – United States, 2016,* including appropriateness of opioid therapy, dosing considerations, and risk assessment of opioid use.
- Describe the pathophysiology of opioid addiction and risk factors for opioid use disorder (OUD) and opioid overdose, the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (*DSM-5*), criteria for OUD, and OUD screening tools.
- Identify signs and symptoms of opioid toxicity and gain an appreciation for the role of naloxone, the drug that is able to reverse opioid overdose.
- Describe techniques and strategies for engaging with patients who may be at high risk of opioid overdose, articulating how these patients may be introduced to naloxone and treatment for opioid use disorder (OUD) as well the pharmacist's ongoing role in public health, health care, and community teams to reduce the impact of the opioid crisis.

Introduction

The number of deaths caused by drug overdose in the United States tripled between 1999 and 2014, reaching a historic peak in 2015 (Rudd, Seth, David, & Scholl, 2016). Opioids were involved in nearly two-thirds of these deaths (Rudd et al., 2016). Economic depression (D'Arrigo, 2017) and rural health disparities (Cicero, Surratt, Inciardi, & Munoz, 2007) have been associated with the increase in opioid overdoses. Although not purposefully, the healthcare system and healthcare providers have also contributed to the current opioid crisis through a "combination of inadequate management of conflicts of interest, morally questionable interactions between regulators and the entities being regulated, questionable policies by government agencies, and unintended consequences of well-meaning efforts to optimize patient care" (Stratton, Palombi, Blue, & Schneiderhan, 2018). Additionally, research has shown that negative attitudes of healthcare providers towards patients with substance use disorders are not only common, but also contribute to suboptimal care for these patients (Van Boekel, Brouwers, Weeghel, & Garretsen, 2013). Surveys conducted in New Mexico and Minnesota have shown that pharmacists, like other healthcare providers, are not fulfilling their potential roles in addressing the opioid crisis and their negative attitudes towards addiction may be causing their patients harm (Bakhireva et al., 2017; Palombi, Melgaard, Hawthorne, Dahley, & Blue, 2018). These surveys have also illuminated the need for further education on appropriate opioid prescribing and education on the opiate antagonist drug naloxone (Palombi et al., 2018).

Pharmacists in multiple practice settings are confronted daily with the need to strike an ethically-acceptable balance between appropriate treatment of a patient's chronic pain and the avoidance of opioid addiction (Stratton et al., 2018). Pharmacists must be aware of how to effectively and appropriately treat pain, how to recognize patients who are taking unsafe doses of opioids, and how to safely and effectively taper at-risk patients off inappropriately high doses of opioids. Pharmacists in multiple practice settings must be familiar with opioid prescribing guidelines so that they can effectively counsel patients and providers alike, and must also be aware of treatment and harm reduction resources that may be helpful to patients who are struggling with opioid use disorder.

This course is intended to educate pharmacists practicing in healthcare systems and community pharmacy settings on the ethical and clinical dimensions of the opioid crisis as they pertain to pharmacy practice. Pharmacists will gain an understanding of appropriate pain management and current guidelines for the prescribing of opioids and will review ways that the safety of a patient's opioid therapy can be evaluated and improved. This course will provide pharmacists with an understanding of the disease state of opioid use disorder and how opioids affect the brain, how the pharmacist can be supportive of patients with opioid use disorder to reduce stigma and facilitate treatment-seeking, and the benefits of medically-assisted treatment and harm-reduction approaches in certain populations of patients.

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CHAPTER 1: INTRODUCTION TO THE OPIOID CRISIS

This chapter provides a historical overview of the opioid crisis in the United States and globally. An understanding of the historical context of the current crisis is necessary to appreciate its complexity and the need for solutions that are multipronged, interdisciplinary, and multimodal and to gain an appreciation for the pharmacist's role in reducing the impact of the opioid crisis.

EPIDEMIOLOGY

Concern is growing about increasing rates of opioid abuse in the United States and globally. An evaluation of global and U.S. trends in substance use will allow for a greater understanding of trends in opioid use and opioid overdose in the United States. This understanding is necessary to appreciate the goals and value of prevention and intervention efforts.

Global trends in substance use

For the past 20 years, the United Nations Office on Drugs and Crime (UNODC, 2017) has provided the international community with information on trends and analysis of drug use and supply while supporting international cooperation and informing international policies. According to the UNODC World Drug Report 2017, approximately 5% of the global adult population, an estimated quarter of a billion people, used drugs for nonmedical purposes at least once in 2015. Approximately 0.6% of the global adult population, about 29.5 million people, suffer from substance use disorders (SUDs). The report also found that in 2015, premature death and disability because of substance use resulted in approximately 28 million years of healthy life lost using disability-adjusted life-years worldwide; of those years lost, 17 million were attributable solely to SUDs. Over the past decade, morbidity and mortality resulting from substance use have increased worldwide. Despite this, fewer than one in six individuals with a SUD access treatment for their disease. The *Diagnostic and Statistical Manual of Mental Disorders,* fifth edition, recognizes substance-related disorders resulting from the use of 10 classes of drugs: alcohol; caffeine; cannabis; hallucinogens; inhalants; opioids; sedatives, hypnotics, or anxiolytics; stimulants; tobacco; and other or unknown substances (American Psychiatric Association, 2013).

Global trends in opioid use

Opioids, including heroin, continue to be the most harmful class of drugs worldwide (UNODC, 2017). Opioid use is associated with increased risks of overdose, acquisition of infectious diseases such as HIV and hepatitis C, and development of other medical and psychiatric comorbidities. According to the UNODC, opioid use disorder accounts for the "heaviest burden of disease attributable to drug use disorders" worldwide (UNODC, 2017, p. 9). In 2015, approximately 70% of the global burden of disease attributable to SUDs – nearly 12 million disability-adjusted life-years – were attributed to opioids.

Global trends in methamphetamine and cocaine use

SUDs related to the use of amphetamines contribute significantly to the global burden of disease attributable to drug use disorders and are second only to SUDs related to the use of opioids (UNODC, 2017). According to UNODC, methamphetamine represents the greatest global health threat of all amphetamines, and the use of methamphetamine worldwide is increasing. Cocaine use, more common in Europe and North America, has been indicated in a growing number of overdose deaths. Much of this is because of the combined use of cocaine and opioids.

Significant comorbidities associated with substance use

People who inject drugs suffer major health consequences that are associated with their substance use. Of the nearly 12 million people worldwide who inject drugs, more than half (6.1 million) suffer from hepatitis C and approximately 1.6 million (one in eight) suffer from HIV (UNODC, 2017). People who inject drugs are also disproportionally affected by tuberculosis infection, likely because of an increase in risk factors for tuberculosis.

Trends in substance use in the United States

SUDs contribute heavily to the burden of disease in the United States. Drug overdose is the leading cause of accidental death in the United States, with 52,404 lethal drug overdoses in 2015 (Rudd, Seth, David, & Scholl, 2016). Beyond loss of life, SUDs are costly to the nation because of crime, increased costs of health care, and lost productivity (U.S. Department of Health and Human Services [HHS], Office of the Surgeon General, 2016).

In 2014, the Substance Abuse and Mental Health Services Administration reported that approximately 20.2 million U.S. adults aged 18 or older had a SUD in the past year; of these adults, 6.2 million had an illicit drug use disorder and 16.3 million had an alcohol use disorder (Lipari & Van Horn, 2017). Of these adults who had a SUD in the past year, one in nine had a SUD and an alcohol use disorder. Only 7.5% of U.S. adults who had a SUD in the past year received treatment for their disorder. The National Survey on Drug Use and Health (NSDUH), an annual survey of the U.S. civilian, noninstitutionalized population aged 12 years or older, has been used to estimate SUDs associated with the use of specific illicit drugs (Lipari & Van Horn, 2017). According to the NSDUH, in 2014, approximately 3.5 million adults had a disorder in the past year related to their use of marijuana, and 1.8 million adults had a disorder related to their nonmedical use of prescription pain relievers. An estimated 900,000 adults had a disorder related to their use of cocaine, and an estimated 600,000 had a disorder related to their use of heroin. Fewer adults had SUDs related to nonmedical use of tranquilizers (420,000), nonmedical use of stimulants (416,000), use of hallucinogens (191,000), nonmedical use of sedatives (114,000), and use of inhalants (57,000). Because individuals can have multiple SUDs from using more than one substance, the categories are not mutually exclusive.

Trends in opioid use in the United States

Opioid addiction is driving the substance use epidemic in the United States, with 20,101 overdose deaths related to prescription pain relievers and 12,990 overdose deaths related to heroin in 2015 (Rudd et al., 2016). Although death rates for the top leading causes of death such as heart disease and cancer have decreased substantially in the last decade, the death rate associated with opioid pain medication has increased markedly (Centers for Disease Control and Prevention [CDC], 2015). Sales of opioid pain medication have increased in parallel with opioid-related overdose deaths (CDC, 2011).

Opioid overdose trends in the United States

Prescriptions for opioids started to increase sharply in the mid to late 1990s (National Institute on Drug Abuse [NIDA], 2014) and were followed by marked increases in nonmedical opioid use, which peaked in the early 2000s (Kolodny et al., 2015). Between 1999 and 2011, hydrocodone use increased more than twofold and oxycodone use rose more than fivefold (Jones, 2013). During this time frame, the mortality rate of opioid-related overdose increased almost fourfold (Chen, Hedegaard, & Warner, 2014).

Drug overdose deaths nearly tripled in the United States between 1999 and 2014 (Rudd et al., 2016). From 2014 to 2015, the CDC found that the death rate from synthetic opioids other than methadone, which includes fentanyl, increased by 72.2% and heroin death rates increased by 20.6%. Rates of death for overdoses involving heroin and synthetic opioids other than methadone increased across all demographic groups, all regions, and in numerous states; opioid overdose rates for those taking natural or semisynthetic opioids increased by 2.6%, and methadone death rates decreased by 9.1%. Although men are more likely than women to die of an opioid overdose, the gap is closing; opioid overdose deaths among women increased more than 400% from 1999 to 2010, compared to 237% among men (CDC, 2011).

Emergency department visits for opioid overdoses rose 30% in all parts of the United States from July 2016 through September 2017 (CDC, 2017. During this same period, some communities suffered a heavier burden from opioid overdose than others: the Midwestern region of the United States saw a 70% increase in opioid overdose between July 2016 and September 2017, and opioid overdoses in large cities increased by 54% in 16 states during this period.

Fentanyl and analogs of fentanyl are involved in an increasing number of opioid overdose deaths in the United States and new fentanyl analogs continue to be discovered (Fogarty, Papsun, & Logan, 2018). Carfentanil, an opioid intended for use in sedating large animals, is the most potent fentanyl analog detected in the United States (O'Donnell, Gladden, Mattson, & Kariisa, 2018). It has 10,000 times the potency of morphine and has been reported in an increasing number of deaths across the United States. Because of the highly potent nature of many analogs, especially carfentanil, multiple administrations of the opioid overdose reversal medication naloxone may be necessary to reverse an overdose involving analogs.

CONTRIBUTING FACTORS TO THE OPIOID CRISIS

The opioid crisis in the United States is a complex problem with numerous contributing factors. Attention has focused on efforts to curb opioid prescribing and on increasing the accountability of pharmaceutical companies that have promoted opioids as a safe, nonaddictive option for the treatment of pain (Dasgupta, Beletsky, & Ciccarone, 2018; Madras, 2017; Stratton, Palombi, Blue, & Schneiderhan, 2018). Still, the social determinants of health – widely accepted as playing a significant role in health – have not been given the attention they deserve when solutions are sought to the opioid crisis (Dasgupta et al., 2018).

Social determinants of health

In 2017, Singh and colleagues explored long-term trend data from the National Vital Statistics System, National Health Interview Survey, National Survey of Children's Health, American Community Survey, and Behavioral Risk Factor Surveillance System to examine racial or ethnic, socioeconomic, rural-urban, and geographic inequalities in health and health care. This study demonstrated that significant social disparities exist in a number of health indicators, most notably in life expectancy and infant mortality, and argues that these disparities in various health outcomes indicate the underlying significance of social determinants in disease prevention and health promotion, which necessitate systematic and continued monitoring of health inequalities according to social factors. Building on this work, Dasgupta and colleagues (2018) explored the role that social determinants have played in the opioid crisis, arguing that the crisis is "fundamentally fueled by economic and social upheaval, its etiology closely linked to the role of opioids as a refuge from physical and psychological trauma, concentrated disadvantage, isolation, and hopelessness" (p. 1).

Economic distress

It has been acknowledged that there are intuitive causal connections between poor health and structural factors including poverty, substandard living and working conditions, and lack of opportunity (Dasgupta et al., 2018). A few scholars have reported that some of the greatest increases in opioid abuse have occurred in areas of economic distress, including the so-called Rust Belt of the United States (D'Arrigo, 2017) and the Iron Range in Minnesota (Collins, 2016), although these reports are not published in peer-reviewed literature. The CDC (2012) has recognized that Medicaid recipients and other low-income populations are at high risk of prescription drug overdose. The HHS (2013) recognizes that people on Medicaid are more likely to be prescribed opioids, at higher doses, and for longer duration, increasing their risk of addiction and its associated consequences; they are also less likely to have access to evidence-based addiction treatment. As Dasgupta and colleagues (2018) point out, "poverty and substance use problems operate synergistically, at the extreme reinforced by psychiatric disorders and unstable housing" (p. 183).

Geographic health disparities

A growing body of research literature acknowledges rurality as an important dimension of social epidemiology and recognizes the vulnerability of rural populations to health-related disparities (Lutfiyya et al., 2012). Opioid misuse has emerged as one among many of the public health-related concerns that appears to have a greater impact on rural than on metropolitan U.S. populations (CDC, 2012; Gale, 2016; Palombi, St. Hill, Lipsky, Swanoski, & Lutfiyya, 2018b). Research has shown that rural drug users have significantly higher odds of lifetime use of opioids and earlier ages of onset for use (CDC, 2012; Cicero, Surratt, Inciardi, & Munoz, 2007). One study found that the rural prescription drug problem was fueled by a cultural acceptance of drug misuse, with two pathways – physical pain and recreation – identified for the misuse of opioids (Leukefeld, Walker, Havens, Leedham, & Tolbert, 2007). Urban communities have also seen an explosion of the opioid crisis, although treatment and harm reduction resources are often more readily available (Cerdá et al., 2013).

Racial health disparities

Racial health disparities are observable and dynamic in the opioid crisis. Research has shown that Native Americans (Murphy et al., 2014) and African Americans (Bechteler & Kane-Willis, 2017) are disproportionally affected by overdose deaths in the United States. Research has also shown an increasing prevalence of opioid misuse in predominantly White, middle-class, and suburban communities (Cole et al., 2017). A study conducted by Cerdá and colleagues in New York City found that Whites were more likely than Blacks and Latinos to overdose on opioids and that deaths occurred most often in neighborhoods with lower rates of poverty, suggesting that access to opioid prescribers may be a contributing factor to the racial disparity. Advantages in healthcare access may have contributed to increased opioid prescribing (Anderson, Green, & Payne, 2009) and availability (Green, Ndao-Brumblay, West, & Washington, 2005) among White patients. Although the opioid crisis has

affected individuals of all races, Netherland and Hansen (2016) have argued for an interpretative frame, which has racialized urban illicit heroin use as an addiction problem of Black and other people of color and medicalized rural opioid misuse as a problem of White people unwittingly hooked by initially legitimate prescriptions for pain.

Ethical factors

In 2000, the Joint Commission on Accreditation of Health Care Organizations introduced pain management standards (Baker, 2017), which required accredited patient care facilities to undertake systematic assessments of pain using measures that had been recommended by the Institute of Medicine (Osterweis, Kleinman, & Mechanic, 1987). This act by the Joint Commission raised treatment of pain to a patient rights issue, and in the Joint Commission's 2001 standards, pain was first mentioned as a fifth vital sign to be assessed in every patient (Baker, 2017). Coinciding with the Joint Commission's presentation of the new pain treatment standards, Purdue Pharma funded nine educational sessions across the country to educate healthcare professionals on the new standards (Lembke, 2016). The Joint Commission agreed to allow only Purdue Pharma to distribute certain education videos and a pain management text and materials, which were also available for purchase through the Joint Commission's website. It has been argued that the Joint Commission, the Federation of State Medical Boards, the U.S. Food and Drug Administration, and the U.S. Drug Enforcement Administration all "failed to manage potential conflicts of interest, leading to a violation of fidelity, the public's trust that these nongovernmental and government agencies practice beneficence – to do good – in the interest of protecting public safety," thus contributing to the opioid crisis in the United States (Stratton et al., 2018, p. 1146).

In 2007, the Centers for Medicare and Medicaid Services (CMS, 2008) introduced its star ratings system as a mechanism by which Medicare patients could assess and compare the quality of care provided by physicians, hospitals, and other providers. The CMS tied star ratings to payments to healthcare providers as a financial incentive for providers to improve their performance. Among the metrics assessed were clinical quality and customer satisfaction (Zavadil, 2015), as well as three questions regarding pain management (CMS, 2008).

The star ratings approach to assessing the quality of pain management resulted in prescribers at facilities receiving high scores for pain management if they were increasing the amounts of opioid pain medications prescribed (Falkenberg, 2013). Falkenberg reported that in at least one instance, a low-scoring hospital had offered Vicodin "goody bags" to patients discharged from the hospital's emergency department in an effort to elicit higher customer satisfaction scores. In response to these concerns and others, the CMS announced the removal of the pain management questions from the Hospital Consumer Assessment of Healthcare Providers and Systems survey in November 2016 (CMS, 2016). In examining the ethical considerations of the U.S. opioid crisis, Stratton and colleagues (2018) have concluded that the crisis "has arisen through a combination of inadequate management of actual or potential conflicts of interest, morally questionable or negligent interactions between regulators and the entities being regulated, some questionable policies by government agencies, and some unintended consequences of well-meaning efforts to optimize patient care" (p. 1150).

Prescribing factors

The previously described ethical factors clearly played a role in patient expectations and opioid prescribing. A report published by the Institute of Medicine (2011) attributed the rise in chronic pain prevalence during the 1990s to greater patient expectations for pain relief, musculoskeletal disorders of an aging population, obesity, increased survivorship after injury and cancer, and increasing frequency and complexity of surgery. During this time, insurers limited coverage of behavioral pain therapy, and pharmaceutical innovation resulted in new modalities of pain treatment, including extended-release formulations, oral dissolving strips, transdermal patches, and nasal sprays (Dasgupta et al., 2018). This, along with pharmaceutical companies downplaying the addictive potential of some opioids and promoting the off-label use of others, lobbying, and physician kickback schemes, is understood to have contributed to the increase in opioid consumption in the United States in the past three decades, which has continued to escalate. In 2012, 259 million prescriptions were written for opioids, which is more than enough to give every American adult a bottle of pills (CDC, 2014).

Research has shown that four in five new heroin users started by misusing prescription painkillers (Jones, 2013). Traffickers of black tar heroin have capitalized on the opioid-dependent population in the United States (Meldrum, 2016), resulting in a shift from opioid pill taking to heroin injecting to achieve the same effect at a lower cost (Mars, Bourgois, Karandinos, Montero, & Ciccarone, 2014; Meldrum, 2016). A 2014 study of people in treatment for opioid addiction confirms what many in SUD treatment already knew, revealing that most respondents (94%) said they chose to use heroin because prescription opioids were more expensive and harder to obtain (Cicero, Ellis, Surratt, & Kurtz, 2014). As a result, heroin overdose deaths have spiked, tripling between 2010 and 2015 (CDC, 2012).

THE ROLE OF THE PHARMACIST

Considerable potential exists for the pharmacist to engage with public health and other healthcare professionals to address the opioid crisis. Understanding and appreciating the historical context of the current opioid crisis, as well as the ways that social determinants of health relate to opioid misuse and overdose, is a critical starting point. Pharmacists must also be aware of the ethical failings of the healthcare system that partially contributed to the current crisis and the patient mistrust of the medical community that resulted from this. Studies have shown that pharmacists may not be fulfilling their public health potential, because many pharmacists do not participate in naloxone distribution to reduce opioid overdose despite legislation that supports this (Freeman et al., 2017; Thornton, Lyvers, Scott, & Dwibedi, 2017), and are not widely supportive of harm reduction techniques that have shown promise in reducing opioid-related morbidity and mortality (Palombi, Melgaard, Dahley, & Blue, 2018a). The HHS (2013) has called attention to pharmacies that are dispensing large quantities of opioids as part of an illegal distribution scheme, as well as to pharmacists who fail to meet their obligation to determine that a prescription was issued for a legitimate medical purpose. Although most pharmacists are attempting to practice appropriately, the HHS (2013) recognizes that in many cases, pharmacies may not have complete information to identify illegal or to flag problem prescribing or doctor- or pharmacy-shopping. For these reasons and others, pharmacists must use the tools available to them to determine whether an opioid prescription is indicated, effective, and safe. Pharmacists in all practice settings must become familiar with the key components of the CDC Guidelines for Prescribing Opioids for Chronic Pain – United States, 2016, so that they can practice at the top of their license as responsible members of the healthcare team, working with other healthcare providers and community members to address the opioid crisis.

In addition to roles in direct patient care and education on appropriate opioid prescribing, pharmacists can participate in initiatives to reduce the impact of the opioid crisis by working with community partners and agencies to establish and support safe medication and syringe disposal. They may become independent naloxone prescribers or join with local healthcare providers in naloxone protocols to ensure that naloxone is available to community members who may need it. Nontraditional pharmacy roles in public health, substance use, drug court, and mental health must also be supported for their potential in improving care for individuals with a SUD while expanding traditional pharmacy practice.

CONCLUSION

Various complex factors have led to the epidemiological trends in increasing substance use globally and increasing opioid use and overdose in the United States. An appreciation for the role of social determinants of health, as well as the opioid-related ethical considerations that pharmacists and prescribers have been challenged with, will lead to finding more effective solutions to reduce the impact of the opioid crisis.

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CHAPTER 2: KEY COMPONENTS OF THE CDC GUIDELINES FOR PRESCRIBING OPIOIDS FOR CHRONIC PAIN – UNITED STATES, 2016

This chapter provides clinicians with a summary of the 2016 CDC Guidelines for Prescribing Opioids for Chronic Pain (Dowell, Haegerich, & Chou, 2016). Treatment of chronic pain conditions continues to be a challenging process for practitioners, because pain is highly subjective. Despite a lack of evidence that supports the long-term use of opioids for the treatment of chronic pain, opioids continue to be prescribed for this condition.

The information provided in this chapter is of particular interest because of the continuing public health epidemic consisting of opioid misuse, abuse, and overdose and the uncertainty encompassing the use of opioid medications for the treatment of chronic pain. An analysis of data from the National Health Interview Survey published in 2015 revealed that approximately 50 million Americans suffer from various types of chronic pain; 25.3 million suffer from daily pain, and 23.4 million report severe pain (Nahin, 2015). Sources of chronic pain in this study included

back pain, fibromyalgia, joint pain, knee conditions, neck pain, and severe headache or migraine.

Prescriptions for opioids started increasing in the mid to late 1990s (National Institute on Drug Abuse [NIDA], 2014), and between 1999 and 2011, hydrocodone use increased more than twofold while oxycodone use rose more than fivefold (Jones, 2013). During this time frame, the mortality rate of opioid-related overdose increased almost fourfold (Chen, Hedegaard, & Warner, 2014). This trend has continued, and the CDC (2018) reported a statistically significant increase in the rate of drug overdose deaths from 2015 to 2016, with percentage changes ranging from 7.4% to 108.6%. The greatest reported prevalence of overdose during this time was occurring in the Northeast, Midwest, and South U.S. Census regions. The CDC also reported research that has shown more than 40% of all U.S. opioid overdose deaths in 2016 involved a prescription opioid, with more than 46 people dying every day from overdoses involving prescription opioids. Because of the continuing challenge in determining the appropriate prescribing practices surrounding opioid use for chronic pain, the goal of this chapter is to provide background information on opioid medications and to review the 2016 CDC opioid prescribing guidelines for chronic pain management.

OPIOIDS FOR THE TREATMENT OF CHRONIC PAIN AND CDC RECOMMENDATIONS

Opioids target mu, kappa, and delta central and peripheral receptors to inhibit the action potentials for both nociceptive pain and perception of pain. Action at these receptors is responsible for supraspinal analgesia, bradycardia, respiratory depression, sedation, and physical dependence. The most common receptor associated with opioid use is the mu receptor, which is concentrated in the brain areas responsible for pain, pain-induced emotional response, and reward. The mechanism of action explains its use as an analgesic to block pain and the euphoric effects that are desired by some individuals, which are associated with the reward system targeted through the mu receptor. The three common classifications of opioids are opium derivatives, semisynthetics, and synthetics. Opioid derivatives include substances such as opium, morphine, codeine, and thebaine. Semisynthetic opioids include heroin, hydrocodone, hydromorphone, and oxycodone. Synthetics include methadone, propoxyphene, meperidine, and fentanyl. Opioid medications come in various formulations, including short acting and long acting and some contain an abuse deterrent to help minimize potential for misuse. In general, immediate-release formulations tend to last 4 to 6 hours, whereas extended-release formulations last 12 to 24 hours. The difference between immediate-release and extended-release formulations is of particular importance for opioid prescribing, because extended-release formulations should be avoided in opioid-naïve patient populations due to increased risk of overdose.

The Centers for Disease Control (CDC) offers recommendations for prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and end-of-life care (Dowell et al., 2016).The guidelines were developed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework and recommendations were made on the basis of a systematic review of the literature while also considering benefits and harms, resource allocation, and values and preferences (Dowell et al., 2016). The GRADE framework allows for evidence to be categorized in a hierarchy, which reflects degree of confidence in the effect of a clinical action on health outcomes. The categories include type 1 evidence, characterized by randomized clinical trials or exceptionally strong evidence from observational studies, type 2 evidence, characterized by randomized clinical trials with notable limitations or strong evidence from observational studies, type 3 evidence, characterized by observational studies or randomized clinical trials with notable limitations, as well as type 4 evidence, characterized by clinical experience and observations, observational studies with important limitations, or randomized clinical trials with several major limitations.

According to Dowel and authors of the CDC Guidelines, "Type 1 evidence indicates that one can be very confident that the true effect lies close to that of the estimate of the effect; type 2 evidence means that the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; type 3 evidence means that confidence in the effect estimate is limited and the true effect might be substantially different from the estimate of the effect; and type 4 evidence indicates that one has very little confidence in the effect estimate, and the true effect is likely to be substantially different from the estimate of the effect" (p. 4). The GRADE framework places recommendations in two categories; Category A recommendations apply to all persons in a group and indicate that most patients should receive the recommended action, while Category B recommendations indicate that there should be individual decision-making for different patients. Category A recommendations "can be made based on type 3 or type 4 evidence when the advantages of a clinical action greatly outweigh the disadvantages based on a consideration of benefits and harms, values and preferences, and costs" while "Category B recommendations are made when the advantages and disadvantages of a clinical action are more balanced" (p. 4).

Preference for nonpharmacological and nonopioid therapies

The first recommendation in the Guidelines for Prescribing Opioids for Chronic Pain – United States, 2016, suggests that nonpharmacological and nonopioid therapies be preferred over opioids for the treatment of chronic pain:

> ***Recommendation #1****: Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate* (recommendation category A, evidence type 3).

Nonpharmacological therapies for chronic pain

Some examples of nonpharmacological treatment strategies include cognitive behavioral therapy, exercise therapy, and complementary therapy, including yoga, meditation, and acupuncture (Dowell et al., 2016). Cognitive behavioral therapy that focuses on training patients in behavioral techniques, and helping patients modify situational factors has had small positive effects on disability and catastrophic thinking (Williams, Eccleston, & Morley, 2012). Exercise therapy has been shown to reduce pain and improve function in chronic low back pain (Hayden, van Tulder, Malmivaara, & Koes, 2005) and to improve well-being, fibromyalgia symptoms, and physical functioning in patients with fibromyalgia (Busch, Barber, Overend, Peloso, & Schachter, 2007). Exercise therapy has also been shown to improve function and reduce pain in patients with osteoarthritis of the knee and hip (Fransen, McConnell, Hernandez-Molina, & Reichenbach, 2014; Fransen et al., 2015); previous guidelines have strongly recommended aerobic, aquatic, or resistance exercises for this group of patients (Hochberg et al., 2012).

Nonopioid alternative therapy options for pain management

Various pharmacological options may be used as nonopioid treatment for pain, including acetaminophen or ibuprofen (Guay, 2001; Maizels & McCarberg, 2005). Supporting this recommendation, a study comparing opioid and nonopioid therapy for moderate to severe chronic back, hip, or knee pain revealed that treatment with opioids was not superior to treatment with nonopioid medications for improving pain-related function over 12 months (Krebs et al., 2018). Skeletal muscle

relaxants may also be used for the treatment of myofascial pain; medications recommended for use include cyclobenzaprine, orphenadrine, or tizanidine. Anticonvulsants provide another medication class that may be used as nonopioid therapy to treat pain; however, many of these medications are used to specifically target neuropathic pain, neuralgia, headache, or migraine. Medications in this class include gabapentin, pregabalin, lamotrigine, carbamazepine, oxcarbazepine, and topiramate. In addition, antidepressants, including serotonin-norepinephrine reuptake inhibitors and tricyclic antidepressants, may be used to treat fibromyalgia, postherpetic neuralgia, chronic musculoskeletal pain, and diabetic neuropathy.

Serotonin-norepinephrine reuptake inhibitors used for nonopioid therapy treatment include duloxetine, milnacipran, and venlafaxine, and tricyclic antidepressants include amitriptyline, nortriptyline, and desipramine. Patients with chronic pain often suffer from concurrent depression (Howe & Sullivan, 2014), and depression can exacerbate physical symptoms including pain (Sullivan, Edlund, Zhang, Unützer, & Wells, 2006); because of this, patients with co-occurring pain and depression are especially likely to benefit from antidepressant medication. When opioids are necessary for prescribing, the guidelines recommend concomitant use of nonpharmacological and nonopioid therapies to supplement pain treatment.

The importance of treatment goals

Recommendation 2 indicates that before the initiation of opioid therapy, providers should discuss treatment goals with all individuals receiving a prescription for pain treatment:

> **Recommendation #2**: *Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and consider how opioid therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety* (recommendation category A, evidence type 4).

These goals should focus not only on the reduction of pain but also on the improvement in daily functioning. To assess pain and function, it is recommended that providers use the Pain, Enjoyment, General Activity (PEG), three-item assessment tool (Dowell et al., 2016). The PEG assessment evaluates a patient's description of pain in the past week, its interference with their enjoyment of life, and its interference with general activity (Krebs et al., 2018). An average score of the three PEG questions is taken at baseline and again throughout treatment at follow-up evaluations to assess the effectiveness of opioid medications. If the follow-up assessment is greater than or equal to a 30% improvement from baseline, the medication is considered clinically effective and therapy may be continued. However, if there is no improvement in function or reduction in pain, treatment of chronic pain with opioids should be reassessed, weighing benefit versus harm. If the patient is not experiencing clinically meaningful improvement, opioid therapy should be tapered to discontinuation (Dowell et al., 2016).

Understanding the risks versus the benefits of opioid therapy

The third recommendation advises discussing known risks and realistic benefits with each patient who is receiving opioid prescriptions:

> **Recommendation #3**: *Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy* (recommendation category A, evidence type 3).

Much of this recommendation focuses on the side effect and safety profile of opioids. Providers are advised to discuss with their patients the realistic benefits in pain reduction and improvement in function and to determine a proper treatment plan. This discussion may include the use of a pain scale from 0 to 10, 10 being the worst pain ever experienced, to help set and determine achievement of goals. The patient should be educated on how the use of the pain scale may help evaluate a decrease in pain. A significant achievement in pain treatment may be getting the patient's pain rating from an eight to a four, effectively reducing their pain to half, but they may not get their pain rating to zero. To address risk, side effects for opioids should be discussed through patient education according to the CDC guidelines, including constipation, dry mouth, nausea, vomiting, drowsiness, confusion, increased risk of infection (immunosuppression), opioid tolerance, physical dependence, withdrawal upon discontinuation, respiratory depression, and risk of opioid use disorder (OUD) development (Dowell et al., 2016). It is also recommended that patients be taught to take medication appropriately and as prescribed, to not share medication, and to keep it out of the reach of children. In addition, patients should be educated on the importance of keeping their medications in a locked, secure location and in properly disposing unwanted or unneeded medications. Various mitigation strategies may be incorporated according to this recommendation, consisting of reviewing information on the prescription drug monitoring program (PDMP) and use of urine drug screens before initiation of treatment and periodically throughout treatment. Although pain treatment contracts are used in clinical practice, the evidence base for this practice is not well established (Chapman, Cruz, & Hutto, 2017) and pain treatment contracts are not included in the CDC recommendations.

Opioid therapy considerations

Opioid formulation selection

Recommendation 4 addresses which formulation of opioid to choose when prescribing for chronic pain, recommending that immediate-release or short-acting opioids be preferred for chronic pain:

> **Recommendation #4:** *When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids* (recommendation category A, evidence type 4).

It is recommended that extended-release or long-acting formulations be avoided when prescribing for chronic pain and that these formulations should be strictly avoided in patients who are opioid naive because of increased risk of respiratory depression and unintentional overdose. When extended-release or long-acting formulations are necessary, methadone and transdermal fentanyl should not be considered a first line of therapy because of their unique risk profiles and increased monitoring requirements, and they should only be prescribed by practitioners that are familiar with the high-profile medications. Methadone, a commonly prescribed long-acting opioid, is particularly problematic, because it has the potential to cause life-threatening arrhythmias (i.e., QT prolongation and torsades de pointes); a baseline electrocardiogram should be evaluated before initiation of therapy to assess corrected QT intervals (Chou et al., 2014). Patients on methadone should be assessed for risk factors, including a history of corrected QT intervals of more than 450 milliseconds or ventricular arrhythmia, and electrocardiograms should be repeated 2 to 4 weeks after initiation of therapy, with a dose increase (i.e., 30 to 40 mg and again when titrating more than 100 mg), or with the development of symptoms of arrhythmia.

Opioid dosing considerations

The fifth recommendation is to always use the lowest effective dose when prescribing opioid medications:

Recommendation #5*: When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when considering increasing dosage to 50 morphine milligram equivalents (MME) or more per day, and should avoid increasing dosage to 90 MME or more per day or carefully justify a decision to titrate dosage to 90 MME or more per day* (recommendation category A, evidence type 3).

It advises that treatment goals and risk versus benefit be re-evaluated when dosages are greater than or equal to 50 MME per day (Dowell et al., 2016). Dosages greater than or equal to 90 MME per day should be avoided, and if necessary, justification should be documented that weighs benefit versus risk for each patient. A retrospective cohort study performed by Dunn and colleagues (2010) found that when comparing patients who received between 1 and 20 MME per day to patients receiving 50 to 99 MME per day, the risk of overdose nearly quadrupled. The risk was even higher in those receiving 100 MME or more per day, with nearly a ninefold increase in risk.

If patients on dosages of at least 90 MME per day do not see clinically meaningful benefit, including both pain reduction and improvement in function, therapy should be carefully tapered and discontinued. This patient population may also benefit from referral to a pain specialist.

Opiates for acute pain

Although the guidelines focus on the treatment of chronic pain, acute pain treatment has the potential to lead long-term treatment as it transitions to chronic pain, and it is recognized for this in Recommendation 6:

Recommendation #6*: Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than 7 days will rarely be needed* (recommendation category A, evidence type 4).

When prescribing opioids for acute pain, such as postsurgical pain and trauma, patients should be given the lowest effective dose and only at an amount that is needed to cover an expected duration of pain. Generally, these quantities are less than or equal to a 3-day supply, and providers should avoid prescribing for 7 days or longer. One study of a representative sample of opioid-naive, cancer-free adults who received a prescription for opioid pain relievers discovered that the likelihood of chronic opioid use increased with each additional day of medication supplied starting with the 3rd day (Shah, Hayes, & Martin, 2017). This study also found that the sharpest increases in chronic opioid use was observed after the 5th and 31st days on therapy, with a second prescription or refill, with a 700-MME cumulative dose, and with an initial 10- or 30-day supply.

Acute pain can often be managed by nonopioid therapies, including ibuprofen and acetaminophen. Providers may benefit from a reminder that opioid medications should not be prescribed if the pain lasts longer than expected. For acute pain management, opioids should be prescribed only for the expected duration of pain to minimize risk of dependence and development of OUD. Long-acting or extended-release formulation should be avoided for treatment of acute pain.

Monitoring patients after opioid initiation

Recommendation 7 recognizes that clinical monitoring for patients initiated on opioid therapy for chronic pain should be provided within 1 to 4 weeks to evaluate potential benefit versus potential harm:

Recommendation #7: *Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower doses or to taper and discontinue opioids* (recommendation category A, evidence type 4).

More frequent or shorter duration between follow-up is indicated for high-risk patients, including those taking long-acting formulations, those taking dosages of at least 50 MME per day or more, those at increased risk of OUD and overdose, or when doses are increased (Dowell et al., 2016). Opioid treatment plans should be evaluated every 3 months to assess risk versus harm and opioids should be discontinued if they are ineffective, the patient develops intolerable side effects, or the patient is at risk of development of OUD. There is no optimal strategy for tapering opioid medications, but patients may benefit from a decrease in the total MME per day by 10% each week until discontinued. Tapers may be done that range from 10% to 25% each week, but the faster the taper to discontinuation, the more at risk a patient may be for developing opioid withdrawal symptoms. Rapid tapers may be initiated in patients with more than 90 MME per day at a decrease of 25% to 50% each week until they reach a dosage of 60 to 80 MME per day. Upon reaching 60 to 80 MME per day, the taper should be reduced to a 10% reduction each week until discontinuation. Individuals diagnosed with OUD may require specific opioid detoxification through referral to a treatment program. As patients are being tapered off opioid medications, pain may still be present and nonopioid therapies should be offered.

Risk mitigation strategies

The opioid prescribing guidelines indicate, in Recommendation 8, that patients at higher risk of opioid-related harm should have mitigation strategies implemented into their treatment to help minimize risk of overdose:

Recommendation #8: *Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥50 MME/d), or concurrent benzodiazepine use, are present* (recommendation category A, evidence type 4).

These high-risk individuals include those with history of overdose, with a substance use disorder (SUD), taking dosages of at least 50 MME per day, or concurrently using benzodiazepines (Dowell et al, 2016). Patients with sleep-disordered breathing, pregnant women, patients with renal or hepatic insufficiency, patients 65 years of age or older, patients with mental health conditions, patients with a SUD, and patients with prior nonfatal overdose are identified in the CDC guidelines as groups that may be at higher risk of opioid-related harm (Dowell et al., 2016). Various mitigation strategies may be used to evaluate whether a person may be at increased risk of development of a SUD and to determine the desired frequency of monitoring. These strategies include the Opioid Risk Tool (Webster & Webster, 2005), the Screener and Opioid Assessment for Patients with Pain (Butler et al, 2006), and the Brief Risk Questionnaire (Jones et al., 2015). Other mitigation strategies include reviewing data within the PDMP and requiring a mandatory urine drug screen before prescribing opioid medications to assess the risk of concomitant use of controlled prescription medications or illicit drug use. Rescue medications, such as naloxone, may also be used to minimize the risk of opioid overdose in individuals with a history of overdose or SUDs, anyone taking additional medications that amplify serious opioid adverse drug reactions, those who have lost

tolerance of a previous dose because of recent incarceration or hospitalization, and patients taking at least 50 MME per day.

Prescription drug monitoring programs

Recommendation 9 of the CDC guidelines urges review of PDMP data before writing each new prescription to ensure that the patient is not receiving additional prescriptions for other controlled substances that may increase the risk of overdose:

> **Recommendation #9**: *Clinicians should review the patient's history of controlled substance prescriptions using state PDMP data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months* (recommendation category A, evidence type 4).

Once a patient is stabilized on a chronic pain therapy regimen, PDMP data should be reviewed every 3 months (Dowell et al., 2016). Statewide PDMPs are usually updated daily with information regarding the dispensing of addictive prescription drugs. These programs were implemented as a public health initiative to minimize diversion, abuse, and misuse of controlled substance prescriptions, as well as reduce the risk of OUD and overdose. Those who are able to access the data include the following: prescribers and their delegates; licensed pharmacists that are involved in direct patient care; designated staff from health-related licensing boards; those authorized to collect, review, and analyze the data; medical examiners; and coroners. Depending on state regulations, public health staff and delegates can access the PDMP, as well as state and federal law enforcement with a valid search warrant. Information collected for the PDMP is considered protected health information and should be treated as covered under the Health Insurance Portability and Accountability Act.

Urine drug screening

In Recommendation 10, the CDC guidelines advise obtaining a urine drug screen before initiating opioid therapy to ensure that the patient is not taking other medications that may increase the risk of respiratory depression and overdose:

> **Recommendation #10***: When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications, as well as other controlled prescription drugs and illicit drugs* (recommendation category B, evidence type 4).

Periodic urine drug screening is also recommended to assess compliance and the use of other controlled substances and illicit drugs; it has further utility in detecting diversion by ensuring that patients are taking the medications being prescribed to them while detecting illicit substances or nonprescribed medications in the urine (Dowell et al., 2016). Urine drug screening is not meant to be a punitive measure but is used to help minimize risk of overdose, which may be because of drug-drug interactions. Urine drug screening varies from clinic to clinic, and it is recommended that practitioners enable themselves to interpret laboratory results within their clinical setting. Things to consider with urine drug screening include drug pharmacokinetics, presence of drug metabolites, patient variability (i.e., body mass, renal impairment, and hepatic function), duration of medication or drug use, pH of urine, and time since last ingestion. Expected results of urine drug screens should be discussed with patients, and results can be corroborated through confirmatory testing at additional cost. For opioid medication, the following medications or drug classes may cause false-positive results and unexpected urine drug screen results: dextromethorphan, diphenhydramine, heroin, poppy seeds, quinine, quinolones, rifampin, and verapamil.

Avoiding concomitant opiates and benzodiazepines

The 11th recommendation of the CDC guidelines urges clinicians to avoid prescribing opioids for patients who are also taking benzodiazepines:

> **Recommendation #11***: Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible* (recommendation category A, evidence type 3).

Common medications that may be seen from the benzodiazepine class include lorazepam, diazepam, midazolam, alprazolam, and clonazepam. Benzodiazepines are Schedule V medications and should be recorded within the PDMP data. Clinicians exercise caution with these medications when used in combination with opioids because of their increased risk of central nervous system depression and subsequent risk of opioid overdose. When a patient is on a dangerous combination of these medications or takes additional medications that suppress the central nervous system, the patient may experience difficulty breathing, bradycardia, hypotension, sedation, coma, or even death. At least one study has shown that concurrent prescriptions for benzodiazepines and opioids are associated with a near-quadrupling risk of overdose death when compared to an opioid prescription alone (Park, Saitz, Ganoczy, Ilgen, & Bohnert, 2015). If benzodiazepines and opioids are taken together and require discontinuation, it is best to start a taper of the opioid medication to discontinuation followed by a slow taper of the benzodiazepine to minimize the risk of respiratory depression and avoid symptoms of withdrawal from both classes of drugs. Symptoms of opiate withdrawal could include headache, abdominal pain, nausea, vomiting, diarrhea, musculoskeletal pain, restlessness, and irritability. Benzodiazepines should be tapered slowly, because abrupt withdrawal could lead to rebound anxiety, hallucinations, seizures, delirium tremens, and death.

Medication-assisted treatment

The 12th and final recommendation of the CDC guidelines encourages providers to offer medication-assisted treatment in combination with behavioral therapies to individuals diagnosed with OUD:

> **Recommendation #12***: Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with OUD* (recommendation category A, evidence type 2).

Providers that wish to prescribe buprenorphine should obtain a waiver from the Substance Abuse and Mental Health Services Administration, authorized by the U.S. Drug Enforcement Administration, enabling them to provide medication-assisted treatment for opioid-dependent individuals (Dowell et al., 2016). Prescriptions must be written for the individual with opioid dependency and written specifically for detoxification as the indication for treatment.

CONCLUSION

This chapter has given an overview of the prevalence of opioid misuse and deaths from overdose, a review of the opioid mechanism of action and available formulations for prescribing, and a complete summary of the 2016 Centers for Disease Control and Prevention prescribing guidelines for opioid use for chronic pain. It is recommended that patients receiving opioids for chronic pain be prescribed no more than 50 MME per day with immediate-release formulations. Any patient on long-term opioid therapy may benefit from frequent re-evaluation of treatment to assess the effectiveness of the medication and the risk of harm. If these medications are not effective, opioid therapy should be tapered to discontinuation to avoid increased risk of development of OUD and death from overdose. Attention to these prescribing recommendations is critical to reduce the morbidity and mortality caused by the opioid crisis in the United States.

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CHAPTER 3: WHAT IS OPIOID ADDICTION?

The *DSM-5* was developed by the American Psychiatric Association (2013) and combined the criteria for opioid abuse and opioid dependence from prior versions of the *DSM* in its new diagnosis of OUD. The American Society of Addiction Medicine (2015) defines addiction as "a primary, chronic disease of brain reward, motivation, memory, and related circuitry," with a "dysfunction in these circuits" being reflected in "an individual pathologically pursuing reward and/or relief by substance use and other behaviors" (p. 3). This chapter examines the pathophysiology of opioid addiction and explores how the *DSM-5* criteria are used in practice.

PATHOPHYSIOLOGY OF OPIOID ADDICTION

Addiction is a brain disease that affects multiple brain circuits, including those involved in motivation and reward, learning and memory, and inhibitory control over behavior (National Institute on Drug Abuse [NIDA], 2012). According to the NIDA, research has shown that some individuals are more vulnerable than others to becoming addicted, depending on the complex relationship of genetics, age of exposure to drugs, and environmental influences. Even though a person may initially choose to take a prescribed or recreational drug, prolonged exposure to drugs affects brain function: an individual's ability to choose may be compromised, the person may seek and consume the drug compulsively, and the individual may lose self-control or willpower. Prescription and recreational drugs of abuse alter the structure and function of the brain and result in changes that persist after drug use has ceased. Opioid dependence occurs when the frequent and repeated use of opioids leads to physiological and structural changes in the brain; once these changes are established, normal brain function requires the presence of opioids. Individuals with genetic vulnerabilities, those who are exposed to chronic stress, those who suffer from comorbid psychiatric conditions, and those who abused drugs during early adolescence are at the greatest risk of becoming addicted to opioids and other drugs of abuse (Volkow & Morales, 2015).

Physiological changes to the brain

Physiological changes to the opioid-dependent brain are numerous and include changes to opioid receptors, messenger enzymes, and kinases, as well as increases in the number of dendritic spines of neurons involved in the reward pathway. Drugs are known to modulate the expression of genes involved in neuroplasticity through epigenetic and possibly RNA modifications, which disrupt intracellular signaling cascades and neuronal circuits, resulting in the long-lasting physiological changes to the brain that are associated with addiction (Volkow & Morales, 2015).

Overexpression of ΔFosB

Overexpression of the gene transcription factor ΔFosB in the nucleus accumbens (NAc) has been shown to play a crucial role in the development of an addiction to opioids by both sensitizing drug reward and amplifying compulsive drug-seeking behavior (Nestler, 2013; Ruffle, 2014). As is the case with other addictive drugs, overuse of opioids leads to increased ΔFosB expression in the NAc.

Drug reward signaling in the brain

The mesolimbic (midbrain) reward system is one of the brain circuits that is activated by opioids. This system generates signals in the ventral tegmental area (VTA) of the brain that result in the release of the chemical dopamine (DA) to the NAc, another part of the brain. This release of DA into the NAc causes feelings of pleasure (Volkow & Morales, 2015; Di Chiara, 2002).

DA neurons located in the VTA and projecting to the NAc are known to have an important role in the processing of reward-related stimuli, including those associated with drugs of abuse (Volkow & Morales, 2015; Wise, 2008). Through their pharmacological effects, drugs of abuse increase the release of DA in the shell subregion of the NAc (Di Chiara, 2002; Volkow & Morales, 2015). Drugs of abuse therefore mimic the phasic DA neuronal firing that leads to fast DA increases and reward signals in the brain (Volkow & Morales, 2015). The large DA increases that are triggered by phasic DA cell firing are needed to stimulate D1 receptors in the NAc.

Opioids affect DA neurotransmission in the NAc via the disinhibition of dopaminergic pathways as a result of inhibiting the □-aminobutyric acid-based projections to the VTA from the rostromedial tegmental nucleus (Bourdy & Barrot, 2012). This interferes with the mechanism that would normally negatively modulate DA neurotransmission. For natural reinforcers such as food or sex, the DA signals triggered by stimuli drive the motivation to get the reward; with their repeated delivery, the DA cells stop firing in response to their consumption (Schultz, 2002; Volkow & Morales, 2015). However, drugs of abuse,

because of their pharmacological properties, continue increasing DA release during their consumption (Volkow & Morales, 2015). In this case, DA in the NAc will increase upon exposure to drug cues, which then triggers the desire to take the drug (craving) during their consumption and in turn results in motivation to continue consuming the drugs of abuse. This phenomenon explains why drugs of abuse are more likely to result in compulsive patterns of consumption and administration than natural reinforcers.

Structural changes to the brain

Neuroimaging has shown both functional and structural alterations in the brain (Goldstein & Volkow, 2011). Goldstein and Volkow suggest that disruption of the prefrontal cortex in addiction underlies both compulsive drug taking as well as addiction-related behaviors. At least one study has shown that chronic intake of opioids including heroin may result in a long-term effect in the orbitofrontal area, which is essential for regulating reward-related behaviors, emotional responses, and anxiety (Ieong & Yuan, 2017a). Neuroimaging and neuropsychological studies by Ieong and Yuan (2017b) have also demonstrated dysregulation of circuits associated with emotion, stress, and high impulsivity in those with opioid use disorder (OUD). Additional studies have shown that chronic opioid abuse affects the temporal insula and thalamus (Goldstein & Volkow, 2011, NAc (Noel & Gratton, 1995), and sensorimotor cortices (Liu et al., 2009).

Opioid tolerance, dependence, and withdrawal

Repeated exposure to increasing doses of opioids alters the brain so that it functions normally when the drugs are present and abnormally when they are not. The results of this alteration include opioid tolerance, the need to take increasingly higher doses of drugs to achieve the same opioid effect, and drug dependence, a susceptibility to withdrawal symptoms (Kosken, 2002). Withdrawal symptoms occur only in patients who have developed tolerance. Opioid tolerance occurs when the brain cells that have opioid receptors on them gradually become less responsive to the presence of opioids; more opioid is needed to stimulate the VTA brain cells of the mesolimbic reward system to release the same amount of DA in the NAc. As a result, more opioid is needed to produce pleasure when compared to that provided in previous drug taking.

Opioid dependence and resulting changes in the locus coeruleus (LC) are implicated in opioid withdrawal symptoms. Neurons in the LC produce noradrenaline (NA) and distribute it to other parts of the brain, where it stimulates alertness, breathing, blood pressure, and other functions (Kosken, 2002). When opioid molecules bind to mu receptors on brain cells in the LC, they suppress the neurons' release of NA, resulting in drowsiness, slowed respiration, and low blood pressure, the known effects of opioid intoxication. When LC neurons are exposed to opioids repeatedly, they adjust by increasing their activity level so that when opioids are present, any suppressive impact they may have had is offset by the heightened activity of the LC neurons; the result is that normal amounts of NA are released and the individual taking opioids feels normal. When opioids are not present to suppress the LC brain cells' enhanced activity, the neurons release excessive amounts of NA. This results in jitters, anxiety, muscle cramps, and diarrhea.

The mesolimbic reward system also contributes to the production of withdrawal symptoms. Opioid tolerance that reduces VTA's release of DA into the NAc may prevent the patient from obtaining pleasure from activities that would normally be rewarding (Koskela et al., 2017). These changes in the VTA and the DA reward systems are known to form an important brain system underlying craving and compulsive drug use.

DSM-5 CRITERIA FOR OPIOID USE DISORDER

OUD is a diagnosis introduced in the *DSM-5* (American Psychiatric Association, 2013). It combined two disorders from the previous edition of the *DSM*, known as opioid dependence and opioid abuse, and it incorporated a wide range of prescribed and recreational drugs of the opioid class. Although OUD is a generic term given in the *DSM-5*, the guidelines indicate that the diagnosis should include the opioid drug being used by the individual (e.g., heroin use disorder for individuals who use the opioid heroin).

Symptoms of opioid use disorder

The diagnosis of OUD can be applied to someone who uses opioid drugs and has at least two of the following eleven symptoms within a 12-month period:

1. Taking more opioid drugs than intended.
2. Wanting or trying to control opioid drug use without success.
3. Spending a great deal of time obtaining, taking, or recovering from the effects of opioid drugs.
4. Craving opioids.
5. Failing to carry out important roles at home, work, or school because of opioid use.
6. Continuing to use opioids despite use of the drug causing relationship or social problems.
7. Giving up or reducing other activities because of opioid use.
8. Using opioids even when it is physically unsafe.
9. Knowing that opioid use is causing a physical or psychological problem but continuing to take the drug.
10. Tolerance for opioids, as defined by either of the following:
    a. A need for markedly increased amounts of opioids to achieve intoxication or desired effect.
    b. A markedly diminished effect with continued use of the same amount of an opioid.
11. Withdrawal symptoms when opioids are not taken:
    a. The characteristic opioid withdrawal syndrome.
    b. The same (or a closely related) substance are taken to relieve or avoid withdrawal symptoms.

(American Psychiatric Association, 2013)

Does anyone on opioids have opioid use disorder?
Not everyone who is on opioids has OUD. Many people are prescribed opioids for pain and do not develop OUD. However, some of these individuals will develop physical tolerance to these prescribed opioids and will experience physical withdrawal symptoms if they do not take the drug. Still, the *DSM-5* explicitly states that these symptoms do not constitute OUD if the individual experiencing them is appropriately medically supervised (American Psychiatric Association, 2013). The *DSM-5* recognizes that addictive disorders are primarily psychological; although someone can develop normal physical responses to prolonged drug exposure; these physical responses – without cravings, difficulty using appropriate dosages, and lifestyle difficulties resulting from taking the drug – do not constitute a disorder.

Gauging the severity of opioid use disorder
An OUD diagnosis is applicable to a person who uses opioids and experiences at least two of the 11 previously listed symptoms in a 12-month period (American Psychiatric Association, 2013). OUD is classified as mild if the individual has two or three symptoms, moderate if the individual has four or five symptoms, and severe if the individual has six or more symptoms.

Screening for opioid use disorder

Numerous screening tools have been developed by experts in addiction. These screening tools can be used to determine whether someone may need to be assessed for OUD.

One of the simplest drug screening tools is the single-item drug screener. This screening tool is used by asking an individual "How many times in the past year have you used an illegal drug or a prescription medication for non-medical reasons?" (Substance Abuse and Mental Health Services Administration [SAMHSA], 2018b, p. 2-7).

The **CAGE** questionnaire is another simple tool that is easy to use in multiple settings and easy to remember using the acronym CAGE as the key letters in four important questions:

- The **C** stands for *cut down.* This can be determined by asking individuals whether they have tried to but could not cut down on their opioid use.
- The **A** stands for *annoyed.* This can be determined by asking individuals whether their family and friends are annoyed about their opioid use.
- The **G** stands for *guilty.* This can be determined by asking individuals whether they ever feel guilty about their use of opioids.
- The **E** stands for *eye-opener*. This can be determined by asking individuals whether they take opioids as an eye-opener in the morning.

(Jovey, 2012)

If an individual answers yes to any of these questions, then that person would benefit from a more complete assessment.

A more complex screening tool is the Opioid Risk Tool (ORT), which calculates the factors that place individuals at greater risk of having a SUD (Webster & Webster, 2005). The ORT measures the following risk factors associated in scientific literature with substance abuse: personal and family history of substance abuse, age, history of preadolescent sexual abuse, and certain psychological diseases. Patients receive scores of 0 to 3 (low risk), 4 to 7 (moderate risk), or more than 8 (high risk), indicating the probability that they will display opioid-related aberrant behaviors.

Screening, Brief Intervention, and Referral to Treatment (SBIRT) is an evidence-based practice that is used to identify, reduce, and prevent use of, abuse of, and dependence on drugs and alcohol (SAMHSA, 2018a). SBIRT is an early intervention approach that targets individuals with nondependent substance use to provide them with effective strategies for intervention before the need for more extensive treatment. The SBIRT model consists of three major components: screening, brief intervention, and referral to treatment. In the screening component, a healthcare professional assesses a patient for risky substance use behaviors using standardized screening tools; the screening can occur in any healthcare setting. The brief intervention involves a health professional engaging with a patient who shows risky substance use behaviors in a short conversation in which feedback and advice are provided. The last component of SBIRT includes referral to treatment or brief therapy for patients whose screening results indicate the need for additional services.

Regardless of which tool is used, every pharmacy or medical practice should determine which screening tools to use and when, how, and by whom they will be administered (SAMHSA, 2018b). Each pharmacy or medical practice should also identify steps to take when a patient screens positive.

CONCLUSION

This chapter has provided an overview of the pathophysiology of opioid addiction and how it relates to a patient's risk of opioid addiction and overdose. OUD is a diagnosis introduced in the *DSM-5*, combining two disorders from the previous edition and incorporating a range of prescribed and recreational drugs of the opioid class. The chapter summarized how the *DSM-5* criteria for OUD are used, identified the eleven *DSM-5* criteria for OUD, and explained how these are used to gauge the severity of the OUD. Several screening tools that can be used to identify OUD and facilitate transitions to treatment were presented and related to pharmacy practice.

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CHAPTER 4: MANAGEMENT OF OPIOID TOXICITY

In 2016, two thirds of the drug overdose deaths in the United States involved an opioid (Centers for Disease Control and Prevention [CDC], 2017b). In comparison to 1999, the number of overdose deaths was five times higher in 2016. This chapter discusses managing an opioid toxicity, including identification of the signs and symptoms of opioid toxicity, how to treat an opioid overdose with naloxone, the available naloxone products for use by laypeople, supportive cares that should be provided during an opioid overdose, legal considerations and trends in naloxone prescribing, and counseling points to consider.

IDENTIFYING THE SIGNS AND SYMPTOMS OF OPIOID TOXICITY

Breathing is slow or absent

Respiratory depression is a hallmark sign of opioid toxicity. It is caused by increased activation of the mu-opioid receptors, particularly those on the brainstem. The brainstem regulates hypercarbia and hypoxemia, and overactivation of the opioid receptors can overcome this regulation pathway, leading to a slower breathing rate that can cause hypercarbia and hypoxemia (Boyer, 2012). Respiratory depression can be identified as a

respiratory rate of 12 or fewer breaths per minute for someone who is not sleeping. A person with a decreased respiratory rate is at risk of reduced oxygenation; ventilation with a bag mask or rescue breathing should be provided to overdose patients with respiratory depression to restore oxygenation and prevent other complications resulting from reduced oxygenation. Tolerance to respiratory depression can develop over time, but not as quickly as analgesic tolerance develops, resulting in a narrowing of the therapeutic window for opioid treatments.

Choking or snoring sounds may be heard

The presence of choking or snoring sounds is often called *Biot's respiration* and is a sign that a person is not breathing adequately (Farney, Walker, Boyle, Cloward, & Shilling, 2008). Biot's respiration is characterized as a pattern alternating between apnea and fast, shallow breathing. The breathing sounds that may be heard during an opioid overdose may be because of inspiratory force against a closed glottis (Boyer, 2012). Alternatively, they could be an indicator of something partially blocking the individual's airway. Either way, the airway should be checked to verify that it is clear by opening the patient's mouth and looking down the throat before beginning ventilation. If inadequate ventilation continues for too long and the breathing pattern worsens, a breathing pattern called a *death rattle* may present, indicating that emergency resuscitation is required immediately (Substance Abuse and Mental Health Services Administration [SAMHSA], 2016). It is critical that a person with inadequate breathing be supported with ventilation and opioid reversal as soon as possible because of the life-threatening severity of this situation.

Individual is not moving and is unresponsive

If touching or moving someone and calling the person's name does not get a response, the pain caused from a sternal rub should be attempted to awaken the individual (Harm Reduction Coalition, 2018b). This is done by rubbing knuckles across the sternum. If such people wake up, they should be monitored and seek medical attention, but if they do not wake up, emergency medical help needs to be called immediately. Sedation because of opioids may be especially pronounced in opioid-naive patients (Benyamin et al., 2008). Sedation because of opioids is poorly understood but is thought to result from a combination of some anticholinergic activity and direct effects of the inhibition of neurons (Benyamin et al., 2008; Dhingra, Ahmed, Shin, Scharaga, & Magun, 2015). Oftentimes, sedation is overcome after a couple of weeks of opioid therapy; therefore, it is most prevalent upon initiation of opioid therapy and during opioid dose escalations (Benyamin et al., 2008).

Skin feels cold and clammy

The cold and clammy feeling of the skin when an individual is experiencing opioid overdose results from peripheral vasoconstriction when an individual's brain has noted that insufficient oxygen is being delivered to this most important organ of the body (Solis, Cameron-Burr, & Kiyatkin, 2017). The vasoconstriction gives the body the opportunity to attempt to hold on to the oxygenated blood centrally, sacrificing peripheral oxygen needs. Vasoconstriction also allows the body to conserve heat in an attempt to keep the most critical organs safe.

Lips and nails are blue

Blue lips and nails are secondary to hypoxia; as previously discussed, it is important to support ventilation during an opioid overdose. This is indicative that a patient is running out of oxygen for the body to stay alive, so ventilation efforts are critical to curb the life-threatening and long-term damage that can occur from hypoxia (Adeyinka & Kondamudi, 2017).

Pupils may be tiny

In a situation involving opioid toxicity, tiny, pinpoint pupils are caused by activation of the opioid receptors in the Edinger-Westphal nucleus of the oculomotor nerve; this nerve controls pupillary constriction and eye movement, and opioid receptor agonism can cause profound constriction of the pupils (Boyer, 2012; Sanders, 2009). Individuals experiencing opioid toxicity will not always have tiny pupils but especially when they have taken more than one substance.

Bowel sounds are absent or reduced

Among the many other areas of the body in which opioid receptors are located, activation of mu-opioid receptors in the gastrointestinal tract lead to decreased contractility of smooth muscle, leading to reduced gut motility (Boyer, 2012). Although this is not a telltale sign of opioid toxicity, it may help identify opioid toxicity if other causes of nonresponsiveness and hypoventilation are also suspected.

TREATMENT OF OPIOID OVERDOSE WITH NALOXONE

Naloxone should be provided to a patient experiencing opioid overdose as soon as possible. This will displace the opioids from the opioid receptors and allow respiration to return, thus reversing the overdose. The individual who received naloxone to reverse an overdose should be monitored for response to naloxone by noting whether the signs previously observed were reversed, especially the return of spontaneous breathing. Even after breathing resumes and the individual who experienced the overdose that was reversed by naloxone appears normal, the individual must be monitored for at least 2 to 3 hours following naloxone administration to be sure re-overdose will not occur as the naloxone wears off. The half-life of naloxone is shorter than that of many opioids; therefore, re-overdose is possible up to about 1-1/2 hours after initial naloxone administration or even hours later for long-acting opioids such as methadone. If an individual does not respond to the first dose of naloxone provided, a second or even a third dose can be given every 3 to 5 minutes. If an individual does not respond to any naloxone doses, it is essential that immediate medical attention is sought to treat and determine the cause, because it may not be an opioid overdose. Upon opioid overdose reversal, a person may begin experiencing unpleasant signs of opioid withdrawal. This may include agitation, combativeness, body aches, diarrhea, tachycardia, fever, runny nose, sneezing, nausea, vomiting, restlessness, and sweating. These side effects of opioid withdrawal are not life threatening, but they can be uncomfortable and are essentially the opposite effects of continuous opioid receptor stimulation.

Pros and cons of various naloxone formulations

See Table 4-1 for detailed comparisons of available naloxone products. One option for practitioners to determine the best product with coverage by the patient's insurance is to use the Formulary Search app or website from Managed Markets Insight & Technology (2018).

Table 4-1: Naloxone Product Summary				
	Intramuscular Injection	**Evzio**	**Nasal Atomizer**	**Narcan**
Strength	0.4 mg/mL.	2 mg/0.4 mL.	1 mg/mL.	4 mg/0.1 mL.
Total naloxone per kit	0.8 to 1.2 mg.	4 mg.	2 to 4 mg.	8 mg.
Rx and quantity	2 to 3 single-use 1-mL vials.	1 two-device pack.	2 2-mL syringes + atomizers.	1 two-device pack.
Dosage	Inject 1 mL (0.4 mg). Repeat in 2 to 3 minutes if needed.	Inject 0.4 mL (one device). Repeat in 2 to 3 minutes if needed.	Spray 1 mL (half of a syringe) into each nostril. Repeat in 2 to 3 minutes if needed.	Spray 0.1 mL (one device) into one nostril. Repeat in 2 to 3 minutes (with the second device into the other nostril) if needed.
Costs*	$	$$$	$$	$$
Unique considerations	Assembly required.	Not covered by most insurance providers, voice instructions.	Assembly required.	Easier to use than an atomizer, improving insurance coverage.

Rx = prescription. *Note*. Table created by Laura Palombi. Reprinted by permission of the author.

Dosage forms with no assembly required

The U.S. Food and Drug Administration (FDA) has approved two naloxone products that do not require assembly for use by laypeople for emergency treatment of opioid overdose in a community setting: Evzio and Narcan. These products are different formulations: an autoinjector for intramuscular or subcutaneous use of naloxone (Evzio) and a spray for intranasal use of naloxone (Narcan). The benefits of using these FDA-approved naloxone kits include ease of use, because they do not require assembly, and vigorously studied pharmacokinetics that suggest the two products are bioequivalent, reaching adequate plasma levels within 15 to 20 minutes of administration to reverse an opioid overdose (Ryan & Dunne, 2018). In Ryan and Dunne's study of laypeople regarding usability of naloxone formulations, it was found that more than 90% of participants successfully delivered naloxone using the FDA-approved products. The FDA-approved products are less fragile than other available products, because they are not packaged in glass. One downside to the FDA products is that they are considerably more expensive; however, prescription insurance companies and patient assistance programs may help make them affordable.

Evzio

Evzio is an autoinjector for intramuscular or subcutaneous use with 0.4 or 2 mg of naloxone upon delivery (Kaléo, 2018; Ryan & Dunne, 2018). The Evzio autoinjector has a voice that instructs a layperson through the process of delivering the medication, which may be helpful in a stressful overdose situation or in patients with limited health literacy. The dose is delivered intramuscularly to the outer thigh as directed by the device – this can be done through clothing as long as it is not too thick (Kaléo, 2018). Evzio provides three devices in each kit: the primary device, a second device in case a second dose is needed, and a training device. Evzio is the most expensive naloxone product on the market; however, Evzio may provide commercially insured patients with zero out-of-pocket copays with its Evzio2You direct-delivery service. This would be an ideal naloxone dosage form for an individual who prefers the assurance of being talked through the steps to take in the event of an overdose, for commercially insured patients, or for a person or caregiver who might have a difficult time manipulating a kit requiring assembly.

Narcan

Narcan in an intranasal spray delivery device with 2 or 4 mg of naloxone delivered upon activation of the device (Ryan & Dunne, 2018). However, patients with altered nasal pathology or chronic intranasal drug use should not be prescribed intranasal products because of potential variability in absorption. This device is easy to use and provides a quick start guide for simple visual instructions to be used in the case of an opioid overdose. Instructions for use include opening the package, holding the device with the thumb on the bottom of the plunger and two fingers next to the nozzle, placing the device into the nostril, and pressing the plunger to release the dose (Adapt Pharma, 2018). Narcan is provided as a pack with two devices in each kit in case a second dose is needed 3 to 5 minutes later. Narcan advertises that 38% of insured people have a zero copay and 77% of insured people have a copay of $10 or less. Like Evzio, this product may be a good option for patients or caregivers who may have stress about or difficulty in manipulating a kit requiring assembly and for any insured patient.

Dosage forms with some assembly required

Several types of naloxone kits can be put together with commercially available products, such as a prefilled syringe with a nasal atomizer for intranasal administration and naloxone unit-dose vials provided with syringes. These naloxone products may be preferred if patients do not have access to prescription insurance because of their more reasonable pricing. Benefits of the kits include titratability of the dose and a reduced cost compared to the branded naloxone products. These products will likely require training of all potential laypeople for successful use, because there is assembly required. The downsides of these dosage forms include assembly, reduced ease of use, fragility, and fewer head-to-head studies comparing the products and their pharmacokinetics.

Prefilled naloxone syringe with nasal atomizer for intranasal administration

The prefilled naloxone syringe is available as a 2 mg/2 mL vial that needs to be assembled with the syringe access and a nasal atomizer. Similarly to the Narcan product, this product should not be used for patients with altered nasal pathology or chronic intranasal drug use because of its dependence on nasal mucous membrane absorption (Ryan & Dunne, 2018). It should also be considered that if the prefilled syringe is being used for intranasal delivery, the atomizer must be included in the kit to ensure the naloxone will be delivered appropriately. The mucosal atomization device is durable medical equipment that has been used off-label for this purpose; it is manufactured by Teleflex and is available online (Teleflex, 2018). This product requires assembly; therefore, it is important for patients and caregivers to be trained on this device if a patient is prescribed it. The prefilled naloxone syringe with nasal atomizer is given by removing the contents from the box, pulling off the two yellow caps (syringe), attaching the nasal atomizer to the Luer-Lock end of the syringe by twisting until tight, pulling off the red cap

of the naloxone vial, and gently screwing the syringe and the naloxone vial together until tight. Once the device is assembled, the atomizer should be inserted into the nostril, and 1 mL, or half of the dose, should be delivered; the other half of the dose should be delivered to the other nostril (Harm Reduction Coalition, 2018a). This can be repeated in 3 to 5 minutes if little or no response is seen and another dose is needed (Harm Reduction Coalition, 2018a). In general, this kit is more affordable than Narcan or Evzio. However, it requires significantly more assembly, which could be difficult for laypeople who are not familiar with making these manipulations. It may be a good option for patients or caregivers who do not want to use needles or are looking for a more affordable option than those that do not require assembly.

Naloxone vial with syringe for intramuscular administration
The naloxone vial with a syringe is the least expensive dosing option, and it may be available in a 4 mg/10 mL multidose vial or 0.4 mg/1 mL single-dose vials (Harm Reduction Coalition, 2018a). Along with the vials, a naloxone kit needs to include one safety syringe for each 1-mL dose and alcohol wipes. The safety syringe must be able to hold at least 1 mL of naloxone and have a 1- to 1.5-inch needle. Assembly is required to draw the naloxone into the syringe: this is done by removing the cap from the naloxone vial, opening a syringe, piercing the vial with the empty syringe, tipping the vial upside down, and using gravity to draw the contents into the syringe; this should amount to 1 mL of naloxone. This formulation is delivered intramuscularly at a 90° angle to the shoulder, thighs, or buttocks. The injection can be given through clothing if needed. After administration, the safety cap should be applied to the syringe and safely discarded into a sharps container. The naloxone vial with syringe is the least expensive naloxone option available; however, it requires the use of needles and assembly. Therefore, it may be a good option for patients or caregivers who are looking for affordability but also feel comfortable with assembling the product and manipulating syringes with needles.

Supportive care considerations in opioid overdose

It is imperative that patients and their caregivers understand that 911 must be called in the case of overdose, even if the individual who is experiencing an overdose responds to naloxone immediately. This is because the patient could fall back into an overdose if the naloxone wears off (Harm Reduction Coalition, 2018b). Many states have Good Samaritan laws protecting bystanders from prosecution when they are acting reasonably to treat an overdose and seek medical attention for the patient.

Other supportive care considerations in creating or dispensing naloxone kits involve the inclusion of rescue breathing masks, rubber gloves, alcohol pads, and visual instructions for assembly or delivery (Harm Reduction Coalition, 2018b). Breathing masks and rubber gloves are important safety tools, especially for the bystander. Visual instructions are provided in Narcan and Evzio kits but are not provided with the prefilled syringe or vials. Because airway support must be provided to patients who are not breathing on their own, it is important for patients and their caregivers to know how to provide rescue breaths to these patients. Rescue breaths are given by laying a person flat on his or her back, tilting the chin up to open the airway, looking down the throat to see whether anything could be obstructing the airway and carefully removing it, plugging the person's nose with one hand and holding the chin open with the other, and giving two regular-sized breaths, making sure to see the chest rising. Two breaths should be repeated every 5 seconds until medical help arrives. Rescue breaths should be started immediately upon recognition that someone is not breathing or not breathing well, because respiratory depression can be life threatening; these breaths should only be paused for a short time to deliver naloxone. It is important for caregivers to stay with the patient until aftercare help arrives, even if the person wakes up. There is a risk of inducing an opioid withdrawal, which can be uncomfortable but generally not life threatening. There is also a risk of a patient re-overdosing because of naloxone's short half-life, depending on the opioids used and their half-life, the patient's liver function, and whether the person uses again after the overdose was reversed.

Pharmacists who enter into naloxone protocols are often required to counsel on supportive care considerations in opioid overdose and fulfill specific educational requirements when dispensing naloxone using a protocol (National Alliance of State Pharmacy Associations, 2018). Pharmacists who dispense naloxone must be well versed in educating patients on supportive care considerations during an opioid overdose and the protections offered by Good Samaritan laws.

LEGAL CONSIDERATIONS FOR PRESCRIBING AND DISPENSING NALOXONE

Naloxone dispensing and prescribing trends in the United States

From the end of 2013 to the middle of 2015, naloxone dispensing from pharmacies increased by 1,170%; however, this was from a low starting point (Davis & Carr, 2017). With opioid overdose deaths still trending up, opioid prescribing rates trending down, and increasing prevalence of heroin use, it is important that pharmacies continue to expand community access to naloxone (CDC, 2017a).

State-specific considerations for pharmacists

All 50 states plus Washington, D.C., allow pharmacists to prescribe and dispense naloxone without a patient-specific prescription from another medical professional in at least one of the options described later (National Alliance of State Pharmacy Associations, 2018). Some states use multiple options for pharmacists to provide patients with naloxone (Prescription Drug Abuse Policy System, 2018). These laws are frequently changing to increase community access to naloxone, so current details for particular states may be found in state laws, statutes, and rules (Davis & Carr, 2017). With any of these considerations of prescribing and dispensing naloxone, pharmacists should use their clinical judgement in providing naloxone and determining the best formulation for each patient. The goal in allowing pharmacists to prescribe and dispense naloxone without patient-specific prescriptions is to remove the barrier of a required medical visit.

Standing order
A standing order for naloxone authorizes pharmacists to provide naloxone to a person as long as predetermined criteria are met as agreed upon with the prescriber. Some states use this language to give authority to nearly all pharmacists in a state to dispense naloxone without a patient-specific prescription from another provider (Davis & Carr, 2017).

Protocol order
A protocol differs from a standing order in that it is developed and promoted by at least one professional board or government agency. For a protocol order, the prescriber of record is typically determined by the state professional board or government agency that has issued the protocol order (Davis & Carr, 2017). Otherwise, it is similar to a standing order.

Naloxone-specific collaborative practice agreements
Naloxone-specific collaborative practice agreements are again similar to standing orders and protocol orders. The collaborative

practice agreement may be sought between a prescriber and a pharmacist or pharmacy for which a relationship has been developed, or it may be statewide (Davis & Carr, 2017).

Pharmacist prescriptive authority
As of July 1, 2017, pharmacists have been given prescriptive authority to dispense or distribute naloxone without a patient-specific prescription in Washington, D.C., and six states: Connecticut, Idaho, Montana, New Mexico, Oregon, and Wyoming (Prescription Drug Abuse Policy System, 2018).

Direct authorization by legislature
As of July 1, 2017, Oklahoma is the only state in which the legislature has directly authorized pharmacists to dispense or distribute naloxone without a patient-specific prescription (Prescription Drug Abuse Policy System, 2018).

ENGAGING WITH PATIENTS AT HIGH RISK OF OPIOID OVERDOSE

In general, it is important for both patients at risk of an opioid overdose and their caregivers to have a strong understanding of what to do in case of an opioid overdose and confidence in their ability to act. Counseling points should include all steps of identifying and treating an opioid overdose as mentioned previously, along with calling 911 to seek medical attention. Patients and caregivers should be counseled on proper storage of naloxone and local Good Samaritan laws (SAMHSA, 2018). According to SAMHSA, patients should be instructed that naloxone only reverses opioid overdoses, not overdose because of other drugs, and does not cause harm if the individual was suffering from something other than an opioid overdose. Patients should also be instructed that in the case of a polysubstance overdose, naloxone will help with the opioid, but medical attention is still necessary for other ingested substances (Lim, Bratberg, Davis, Green, & Walley, 2016).

Naloxone products should be stored in accessible locations at room temperature and protected from light. These products should also be checked regularly for expiration (College of Psychiatric and Neurologic Pharmacists, 2018). However, if the only product available in the case of an overdose is an expired product, it should still be used even though it may not work as effectively. Good Samaritan laws have been developed to legally protect the people who experience or witness an overdose from opioids to encourage individuals to safely seek medical care (SAMHSA, 2018). These laws differ in every state, but as of July 2017, SAMHSA reported that 40 U.S. states and Washington, D.C., have implemented some form of Good Samaritan laws. Unfortunately, there is a lack of awareness of these laws in many communities, so pharmacists must be aware of these protections and disseminate the information to individuals getting naloxone. In addition, the range of protections varies by state, so familiarity with local laws can help pharmacists best serve their patients.

Counseling considerations for individuals at risk of opioid overdose

Individuals at risk of opioid overdose can practice harm reduction strategies to reduce the risk of opioid overdose. These include avoiding mixing medications such as opioids with other substances such as benzodiazepines and alcohol (Harm Reduction Coalition, 2018b). Other strategies include being aware of their tolerance, knowing the quantity and quality of what they are taking, avoiding using alone, understanding the risks of modes of administration, and understanding that they have an increased risk if they have experienced a previous nonfatal overdose. Tolerance – how much of a drug a person's body can process – can be reduced if a person stopped using a drug for some time or if substances are mixed. If a prescription opioid dose has increased, it is important for patients to understand that the side effects may also be enhanced; similarly, if street drugs are used, it is impossible to know how much of a drug may be in a dose. Patients known to be using opioids (including heroin) recreationally should be advised to avoid using opioids when they are alone, because if an overdose were to occur, there would not be anyone present to call for medical help or attempt to reverse the overdose with naloxone and supportive care. Comorbidities such as liver or lung diseases can increase an individual's risk of fatal overdose because of the body's ability to metabolize opioids (liver) and support respiration if respiratory drive is reduced (lungs). Unfortunately, patients may use multiple nonprescribed modes of administration of opioids, such as snorting, injecting, or rectal administration, that can increase the amount of drug in a shorter period than the indicated administration; therefore, a higher risk of overdose may be present. Overall, it is important to limit risks by practicing harm reduction strategies to avoid an opioid overdose.

Counseling considerations for family members and friends

Family members and friends of individuals who are at risk of an opioid overdose should be aware of how to treat an overdose if they witness it. They should also support their loved one to seek an opioid treatment program that can help that person taper off of the medications (SAMHSA, 2018). It is important for caregivers to also take care of themselves, so finding a support network for themselves and loved ones may be helpful. Support groups may be found through healthcare providers or systems, 12-step recovery programs, educational institutions, faith-based support groups, government agencies, and community support.

CONCLUSION

When managing opioid toxicity, it is important for laypeople to be able to identify the signs and symptoms of an opioid overdose, be confident and able to respond with supportive care and naloxone when available, successfully deliver naloxone to the victim, and understand their legal role. Signs and symptoms of opioid toxicity include slow or absent breathing, choking or snoring sounds, unresponsiveness, cold or clammy skin, blue lips and nails, tiny pupils, and absent or diminished gut motility sounds. Laypeople should respond to an opioid overdose with rescue breathing to supply the victim with oxygen and naloxone to antagonize the opioid and restore breathing. Naloxone delivery depends on the naloxone formulation; this should be chosen based on patient and caregiver preference and comfort. It is also important for pharmacists to disseminate information regarding the legal roles of caregivers and Good Samaritans and their protections in caring for a life-threatening toxicity. Because pharmacists play a unique role in expanding patient access to health care, they must be able to share this information with patients who are seeking naloxone for themselves or their loved ones. Pharmacists must feel confident in educating patients and other providers on the topics discussed in this chapter if they are to affect the opioid crisis.

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CHAPTER 5: PATIENT AND POPULATION CARE TO REDUCE THE IMPACT OF THE OPIOID CRISIS

This chapter provides an overview of the pharmacist's role in addressing the opioid crisis, with a focus on community, ambulatory, and institutional pharmacy practice. Many practicing pharmacists have roles in substance use and harm reduction that are developed well beyond the scope of this chapter; this chapter serves as an introduction to public health and harm reduction for pharmacists who strive to develop and expand their current roles.

TECHNIQUES AND STRATEGIES FOR ENGAGING WITH HIGH-RISK PATIENTS FOR SECONDARY PREVENTION

Multiple screening tools may be beneficial for identifying patients with high-risk opioid use to direct them to secondary prevention. Some of these tools have been developed for specific populations, while others are more generalizable. The commonly used tools include the Opioid Risk Tool; Revised Screener and Opioid Assessment for Patients With Pain; Current Opioid Misuse Measure; Addiction Behaviors Checklist; Alcohol, Smoking and Substance Involvement Screening Test; and National Institute on Drug Abuse-Modified Alcohol, Smoking and Substance Involvement Screening Test. The screening tools are outlined in Table 5-1 (Duber et al., 2018). In addition, SBIRT, which stands for Screening, Brief Intervention, and Referral to Treatment, is an evidence-based screening tool that is used to identify, reduce, and prevent problematic use of, abuse of, and dependence on alcohol and illicit drugs (Substance Abuse and Mental Health Services Administration [SAMHSA], 2018a).

Table 5-1: Opioid Use Disorder Screening Tools

Tool	Author	Population	Methods	Screening Tool Characteristics
Opioid Risk Tool (ORT)	Webster (2005)	Newly enrolled adult patients at a pain clinic. Administered before beginning of opioid therapy for pain management.	Brief self-report, 10 questions (yes, no).	Assesses personal and family history of substance abuse, H/O sexual abuse, and psychological disease.
Revised Screener and Opioid Assessment for Patients With Pain (SOAPP-R)	Butler (2008) Reyes-Gibby (2016) Weiner (2015)	Adult patients with chronic noncancer pain treated at pain clinics. Assessed for feasibility in the ED.	Self-report. 24 questions. Likert 5-point scale ("never" to "very often").	Short (95% completed in <5 min), easy to score, assessed in the ED setting. Sensitivity 0.81. specificity 0.68 (using a cutoff score of 18).
Current Opioid Misuse Measure (COMM)	Butler (2008)	Adult noncancer chronic pain patients. Assesses risk for aberrant drug-taking behavior before the init iation of opioid therapy-chronic pain patients.	17 items. patient self-assessment Likert 5-point scale.	Sensitivity 0. 77. specificity 0.68 (using a cutoff score of 9).
Addiction Behaviors checklist (ABC)	Wu (2006)	Adult patients with chronic pain already prescribed opioids or sedative analgesics.	20 questions (yes, no).	Assesses addictive behaviors exhibited "since the last visit" and "within the current visit." Longitudinal assessment. Sensitivity 0.88, specificity 0.86 (using a cutoff score of 3).
Alcohol, Smoking and Substance Involvement Screening Test (ASSIST V 3.0)	WHO (2002)	Adults with no history of substance use, history of use, and history of dependence.	Interviewer-administered pencil-and-paper questionnaire and screens.	Addresses multiple addictive substances, including opioids. Sensitivity and specificity developed for use/abuse and abuse/dependence. Sensitivity 0. 75, specificity 0.65 (for abuse/dependence).
NIDA-Modified Alcohol, Smoking and Substance Involvement Screening Test (NIDA-m-ASSiST)	NIDA Blow (2017) Bogenschutz (2014) Macias-Konstantopoulos (2014)	Intended for adults in the primary care setting. Used effectively in the ED.	Patient interview or online self-assessment.	Patients are asked about street opioids, such as heroin. and misuse of prescription opioids separately. Has not been validated.

ED = emergency department; H/O = history of. Note. Reprinted with permission from Duber, H. C., Barata, I. A., Cioè-Peña, E., Liang, S. Y., Ketcham, E., Macias-Konstantopoulos, W., … Whiteside, L. K. (2018). Identification, management, and transition of care for patients with opioid use disorder in the emergency department. *Annals of Emergency Medicine, 72(4), 420-431.* doi:10.1016/j.annemergmed.2018.04.007.

Although SBIRT and other screening tools can be used by pharmacists who wish to more purposefully focus their practice on the care of individuals with substance use disorders (SUDs) or increase their referral of patients with SUDs to treatment, there are many other ways in which pharmacists can engage more fully in the care of patients at risk of opioid overdose.

Eliminating stigma associated with substance use disorders and risk of opioid overdose

When interacting with patients who may have a SUD or are at risk of opioid overdose, it is important to eliminate stigma from the conversation. Stigma is defined as an attribute, behavior, or condition that is socially discrediting (Kelley, Wakeman, & Saitz, 2015). Stigma is a key concept in SUDs, because it is a major barrier to seeking help: of the 23 million Americans who meet criteria for a SUD each year, only 10% access treatment (SAMHSA, 2013, 2014). Factors that contribute to stigma associated with OUD and treatment options include the following: misunderstanding of addiction as a moral weakness or choice overshadowing its conception as a medical illness, separation of general health care and health care for an opioid or SUD, society's and healthcare professionals' use of derogatory terminology, and the criminal justice system's criminal judgement rather than medical treatment (Olsen & Sharfstein, 2014).

Historically, SUDs have been treated apart from other health care, and some support groups believe that medication used to treat the addiction suggests a lack of willpower and may go to the extent of shunning a person receiving medication-assisted treatment (MAT) from recovery groups (Olsen & Sharfstein, 2014). Patients may feel stigmatized if they are required to seek medical care from multiple providers to meet all their healthcare needs, and with a common lack of coordinated care between clinics and practitioners, this may be a significant barrier for patients to use treatment options. Healthcare professionals should be setting an example by minimizing stigmatizing language rather than perpetuating hurtful labels that harm patients. Lastly, the criminal justice system does not always provide or refer to medical treatment or support during transitions into the community to fully support a patient in recovery. Overall, by providing an understanding environment without stigma, patients at risk of opioid overdose or those with OUD may be more willing to discuss their needs.

Kelley and colleagues (2015), recognizing how research is revealing that one contributory factor to the perpetuation of stigma may be the type of language used, call upon health professionals to recognize how their language surrounding SUDs may be contributing to the substance use crisis in the United States. Purposeful use of the more medically and scientifically accurate term *substance use disorder,* rather than use of terms such as *substance abuser, junkie,* or *drug seeker* are necessary to reduce the stigma associated with SUDs. Avoiding terms such as *dirty* and *clean* and using terms such as *positive* and *negative* when referring to a urine drug screen, for example, are simple ways to eliminate language that contributes to stigma. Kelley and colleagues argue that the language clinicians and providers often use in discussing SUDs is neither professional nor culturally competent and perpetuates stigma.

Introducing high-risk patients to naloxone

Some pharmacists may find it difficult to start a conversation about opioid overdose risk, but this is one example of a crucial conversation that needs to be initiated for the patient's safety. Some pharmacists find it easiest to approach the conversation in the same way that they would for other medical conditions that require a medication to prevent condition-related harm, such as a glucagon kit for a patient at high risk of hypoglycemia or an epinephrine autoinjector (EpiPen) for a patient at high risk of anaphylaxis.

Guidance for clinicians who seek to increase their effectiveness in working with patients who have a SUD has focused on the importance of honesty in the patient interaction, encouragement to explore MAT, and the critical importance of treating a SUD as a disease rather than a moral failure (Parks, 2016). Clinicians and pharmacists who wish to effectively introduce high-risk patients to naloxone as an opioid overdose reversal agent should choose to emphasize that opioid medications carry certain risks, but not that the patients themselves are risky, when framing the conversation.

By focusing on the risks of the opioid that a patient may be taking, a prescriber can focus on the intervention that will reduce the associated risk, thus maximizing patient safety (Parks, 2016). Similarly, by focusing on risks in coordination with comorbid conditions (sleep apnea and pneumonia), interacting medications (benzodiazepines), alcohol use, or even the risk of children or grandchildren accidentally getting into the medication, patients may better understand the effects that reduced respiratory drive may cause. Healthcare professionals may also be helping patients by ensuring that they understand what an opioid overdose may look like; they may perceive an overdose as being the result of illicit drug use or overusing prescription medications, but an overdose can occur at prescribed doses and may seem more like an adverse reaction of sleepiness without realizing that respiratory drive has been reduced (Parks, 2016). It is important for patients to realize that the healthcare professional's main concern is for their safety and that naloxone may be a necessary tool that they can keep as a safety net in case it were ever needed.

Referring high-risk patients to treatment for opioid use disorder

Pharmacists should be aware of which patients may be at high risk of a SUD and may benefit from a referral. Referral options may include inpatient treatment, outpatient treatment, MAT, and obstetrics and infant care for neonatal abstinence syndrome (NAS). It has been estimated that between 11% and 40% of individuals with a SUD receive evidence-based treatment to help them reach a stage of recovery (Haffajee, Bohnert, & Lagisetty, 2018; Thompson, Rao, Hayes, & Purtill, 2018). Pharmacists should be familiar with local resources for SUDs and SAMHSA's Behavioral Health Treatment Services Locator Tool (2017a) and National Helpline at 1-800-662-HELP (4357) or 1-800-487-4889 (for TTY; 2017b). This tool helps to identify services based on particular types of care, service settings, type of treatment program, accepted payment or insurance and assistance, programs for specific patient groups, age, gender, other addictions, languages, and geography. One downfall is that it does not identify services that have room to take new clients (SAMHSA, 2017b).

Inpatient treatment

Inpatient SUD treatment may take place in a hospital or in a specialized mental health or SUD treatment facility, and treatment duration may range from acute care to extended treatment, often determined by insurance coverage and needs (SAMHSA, 2018b). One study suggests that SUD treatment of inpatients admitted voluntarily or compulsorily led to a 61% or 37% reduction in frequency of use, respectively (Pasareanu, Vederhus, Opsal, Kristensen, & Clausen, 2016). Pasareanu and colleagues found that voluntary SUD treatment led to better outcomes, but outcomes were improved whether patients were admitted voluntarily or compulsorily.

Outpatient treatment

Outpatient treatment options may include counseling, intensive outpatient treatment, recovery support services, 12-step fellowship, and peer support (SAMHSA, 2018b). Outpatient treatment options likely include a combination of services that may be beneficial in supporting the patient through

recovery; they usually provide individual, group, or both types of counseling options. Counseling therapies used in outpatient treatment may include cognitive behavioral therapy, contingency management, and motivational enhancement therapy; these are used to assist individuals with a SUD in identifying stresses and situations that put them at risk of using, incentivize their positive behavior, and build motivation and commitment to maintain recovery efforts. Intensive outpatient treatments may require attendance in meetings, counseling sessions, reflection, and submission for drug testing at regular intervals. SAMHSA notes that recovery support services may be available in communities or through support from family and friends, including employment, housing, educational, and transportation support; faith-based support; mentoring or coaching; community outreach and engagement programs; staffing at peer-run recovery, crisis services, and centers; and education for recovery and wellness. Twelve-step programs are often a key component of outpatient recovery programs; these programs serve as accessible and no-cost resources for individuals with SUDs (Donovan, Ingalsbe, Benbow, & Daley, 2013). Evidence has shown that early involvement in a 12-step program, in the form of meeting attendance and engagement in recovery activities, is associated with better substance use and psychosocial outcomes, in addition to reduced healthcare costs.

Medication-assisted treatment

MAT plays an important role in treating OUD to help minimize the effects of opioid withdrawal and cravings. MAT has shown value in increasing treatment retention, reducing the risk of relapse, improving patient survival, improving birth outcomes, and improving an individual's ability to find and maintain employment (SAMHSA, 2018b). Current options for MAT include methadone, buprenorphine, and naltrexone.

Methadone

Methadone is a synthetic opioid agonist that can be used for treatment of OUD in the detoxification or maintenance phases of treatment. Because this medication is a mu receptor agonist, overdose and respiratory depression are possible, along with analgesia without euphoric effects. When used as a treatment of opioid dependence, methadone can only be dispensed by opioid treatment programs certified by the SAMHSA and approved by the designated state authority (IBM Micromedex, 2018b). According to IBM Micromedex, methadone is typically dosed at a maximum of 40 mg daily in divided doses to start, and the dose can be slowly tapered up to reduce symptoms of withdrawal. Initially, 20 to 30 mg of methadone is orally administered when there are no signs of sedation or intoxication and the patient shows signs of withdrawal; an additional 5 to 10 mg may be given 2 to 4 hours later if needed. The dose should be adjusted cautiously over the first week based upon control of withdrawal symptoms 2 to 4 hours after a dose. A lower initial dose should be given to patients with low expected tolerance (e.g., have not taken opioids for more than 5 days). Maintenance dosages typically range from 80 to 120 mg per day and are determined when opioid withdrawal is prevented for 24 hours. When reducing a dose to taper therapy down, dose adjustments should be reduced by about 10% every 10 to 14 days to prevent significant withdrawal. Slow dosing adjustments are important because of methadone's nonlinear pharmacokinetic profile, multiple active metabolites, and variations in cytochrome P450 activity. Side effects are similar to those of other opioids and may include nausea, vomiting, sedation, respiratory depression, and constipation. Methadone is supplied in solution for injection, solution for oral delivery, oral tablets, and oral tablets for suspension; it is the only MAT that can be used in pregnant or breastfeeding women, but it needs to be carefully managed by the prescriber.

Buprenorphine

Buprenorphine is a mixed opiate agonist-antagonist agent with partial agonistic effects at the mu-opioid receptor and antagonist effects at the kappa-opioid receptor (IBM Micromedex, 2018a). The mu-agonistic effects can cause respiratory depression, sedation, and analgesia, while the kappa antagonism prevents cravings for opioids. According to IBM Micromedex, some common side effects of buprenorphine include nausea, vomiting, constipation, application or injection site reaction, headache, and dizziness and are similar to those of other opioids. Buprenorphine for OUD treatment is typically high in dose and comes in multiple drug delivery or drug-combination formulations; some common drug delivery formulations include transdermal patches, buccal films, subcutaneous implants, and solution for subcutaneous injection. Buprenorphine is sometimes combined with naloxone for formulations to reduce the risk of respiratory depression; the most common of these formulations include Suboxone (buprenorphine and naloxone sublingual film; U.S. Food and Drug Administration [FDA], 2018d), Bunavail (buprenorphine and naloxone buccal film), and Subutex, a combination sublingual tablet (IBM Micromedex, 2018a). Combination formulations were designed to reduce the risk of respiratory depression and sedation.

Naltrexone

Naltrexone is a pure opioid antagonist blocking the effects of opioids by competitively binding their receptors. Side effects of naltrexone are similar to those of opioid withdrawal and include abdominal upset, nausea, body aches, difficulty sleeping, headache, and nervousness (IBM Micromedex, 2018c). Naltrexone is available in oral and intramuscular formulations. According to IBM Micromedex, the generic oral formulation can be used for rapid opioid detoxification or withdrawal (with clonidine or buprenorphine) with a daily dose escalation, or it can be used in maintenance therapy with daily, every other day, or every third day dosing schedules. The intramuscular formulation, Vivitrol, is delivered as an extended-release suspension for gluteal injection every 4 weeks. To receive intramuscular naltrexone treatment, patients must be abstinent from using opioids or alcohol for at least 7 days before beginning therapy (IBM Micromedex, 2018d).

New MAT medications

There will likely be new MAT agents and routes of administration on the market in the next few years, but options are limited. In April 2018, the FDA announced the encouragement and support for developing new MAT treatment options for people with OUD (FDA, 2018c).

Obstetrics and infant care for neonatal abstinence syndrome

Women who are pregnant and use opioids – whether or not they receive opioids through a valid prescription – require comprehensive obstetric care with MAT. Collaborative approaches to supporting women who are pregnant and using opioids have shown success. One such program is the Perinatal Assistance and Treatment Home (PATHways) program in Kentucky, which has demonstrated positive outcomes in treating OUD among pregnant women to minimize the burden of NAS (Adams, 2017). The PATHways program supports pregnant women by treating their OUD with MAT, smoking cessation, training for motherhood skills, and other education for mothers to best take care of their babies.

Harm reduction strategies to improve public health

Harm reduction approaches have shown promise in reducing morbidity and mortality associated with the opioid crisis. Harm reduction techniques are a set of strategies used to reduce the negative consequences of substance use and are based on social justice properties to build respect of those who are affected (Harm Reduction Coalition, 2018). The Harm Reduction Coalition, a national advocacy and capacity-building organization that strives to educate the public on the benefits of harm reduction, has developed principles that are central to practicing harm reduction (see Figure 5-1).

Figure 5-1: Principles of Harm Reduction

- Accepts, for better and or worse, that licit and illicit drug use is part of our world and chooses to work to minimize its harmful effects rather than simply ignore or condemn them.
- Understands drug use as a complex, multifaceted phenomenon that encompasses a continuum of behaviors, from severe abuse to total abstinence, and acknowledges that some ways of using drugs are clearly safer than others.
- Establishes quality of individual and community life and well-being – not necessarily cessation of all drug use – as the criteria for successful interventions and policies.
- Calls for the nonjudgmental, noncoercive provision of services and resources to people who use drugs and the communities in which they live to assist them in reducing attendant harm.
- Ensures that drug users and those with a history of drug use routinely have a real voice in the creation of programs and policies designed to serve them.
- Affirms drugs users as the primary agents of reducing the harm of their drug use and seeks to empower drug users to share information and support one another in strategies that meet their conditions of use.
- Recognizes that the realities of poverty, class, racism, social isolation, past trauma, sex-based discrimination, and other social inequalities affect both people's vulnerability to and their capacity for effectively dealing with drug-related harm.
- Does not attempt to minimize or ignore the real and tragic harm and danger associated with licit and illicit drug use.

Note. From Harm Reduction Coalition. (2018). Principles of harm reduction. Retrieved from http://harmreduction.org/about-us/principles-of-harm-reduction/.

Although sometimes seen as controversial because of concerns that harm reduction approaches promote substance use (Ti & Kerr, 2014), widespread support for harm reduction programs as an essential response to the harm caused by drug use continues to grow (Ti & Kerr, 2014; World Health Organization [WHO], United Nations Office on Drugs and Crime, and Joint United Nations Programme on HIV/AIDS (UNAIDS), 2013). International health organizations including the WHO and the UNAIDS recommend harm reduction programs as best practices for reducing morbidity and mortality among people who inject drugs (WHO, 2013). The WHO and UNAIDS comprehensive HIV prevention package for the prevention, treatment, and care of HIV among intravenous drug users recommends the provision of sterile needles and syringes, as well as opioid substitution therapy; responding to this recommendation, public health and nongovernmental organizations in various settings have implemented these programs (Beyrer et al., 2010; Strathdee & Stockman, 2010).

Tertiary prevention and emergency response

Harm reduction strategies including naloxone and syringe access serve as tertiary prevention and emergency response to the opioid crisis. Pharmacists can work with their community to decrease opioid-associated morbidity and mortality by dispensing naloxone and participating in syringe access programs.

Naloxone

Naloxone is the opioid antagonist that can be used to reverse an acute emergency opioid toxicity. It works by outcompeting opioids at the mu-opioid receptors – binding to those receptors and blocking them – to prevent the opioids from causing fatal respiratory depression. The removal of opioids from the opioid receptors allows the overdose victim to resume normal breathing; respiratory depression is the usual cause of death in opioid overdoses. Pharmacists who are unfamiliar with the drug naloxone and laws regarding naloxone in their state would be advised to pursue additional education in this critical area. Naloxone is available by prescription and often is distributed in the community without a prescription; it may be administered by laypeople or medical professionals. Individuals who experience an opioid overdose reversed by naloxone must be referred to medical care even after breathing resumes and they appear to have returned to a normal state; naloxone does not destroy the opioid but rather outcompetes it at the mu-opioid receptor, so individuals are at risk of re-overdosing once the naloxone wears off. It is also critical for pharmacists to counsel on the importance of rescue breathing during an opioid overdose situation.

Despite concerns that naloxone distribution promotes substance use and overdose, research does not support this myth. Wagner and colleagues (2010) found in a study of injectable drug users that 53% reported decreased drug use 3 months after participating in an opioid education and naloxone distribution program. Walley and colleagues (2013) in Massachusetts found that education of opioid users at risk of overdose, and their family and friends, had a significant reduction (27% to 46%) in the adjusted rate ratio of opioid overdose. Doe-Simkins and colleagues (2014) showed no change in heroin use 30 days after take-home naloxone.

Syringe access

The provision of access to clean syringes has been beneficial in preventing the spread of infectious diseases, including HIV and hepatitis C. Pharmacies have been recognized as a viable source of sterile syringes for people who inject drugs because of increased availability compared to syringe exchange programs, which can reduce the prevalence of HIV and other communicable diseases and have a measurable public health impact (Friedman, Perlis, & Des Jarlais, 2001; Siddiqui et al., 2015). Syringe access programs have been studied in multiple settings and have been determined to be effective options in reducing the incidence of HIV by 80% for those who use drugs, saving taxpayer money, lowering healthcare costs, and preventing hepatitis C (Harm Reduction Coalition, 2010). Research has demonstrated the safety and efficacy of needle and syringe exchange programs as a lifesaving, harm-reducing public health intervention (Cooper et al., 2012). Research conducted by Vlahov and Junge (1998) documents that needle exchange and syringe access programs do not result in increased drug use among participants or in the recruitment of first-time drug users; when "legal restrictions on both purchase and possession of syringes are removed, IV drug users will change their syringe-sharing behaviors in ways that can reduce HIV transmission" (p. 76).

Safe medication storage and disposal

All medications should be stored safely to prevent accidental ingestion, integrity of the product, and even theft to prevent a potential overdose (Centers for Disease Control and Prevention, 2016). Unneeded, unused, and expired medications should be disposed of safely to reduce the risk of having excess medication around (FDA, 2018a). According to the FDA, some options for safely disposing of medications include medication takeback options, disposal in the trash, or flushing certain dangerous medications down the toilet. The preferred route of disposal for medication is through medication takeback, which occurs through permanent collection sites that may be found in law enforcement facilities or pharmacies or through periodic events such as National Prescription Drugs Take-Back events. Permanent collection sites registered with the U.S. Drug Enforcement Administration (DEA) can be located by calling 1-800-882-9539 or visiting the Controlled Substance Public Disposal Locations Search Utility hosted by the Diversion Control Division through the DEA (DEA, 2018). If drug takeback programs are not available, the risk of holding on to dangerous

medications such as opioids may outweigh the risk of small amounts of these medications in the environment, so it may be advised to discard them in household trash or in the toilet. Patients who wish to discard medications in the trash should be advised to mix the medication with an unpalatable substance such as coffee grounds, cat litter, or dirt and then seal the mixture in a plastic bag before throwing it away. Commercial drug deactivation systems such as Deterra (2018) are another option to safely disposing of unwanted medications that end up in household trash. Disposal information for specific medications can be found by visiting the FDA's Drugs@FDA database, searching for the particular medication, clicking on the label of the drug, and searching for the term *disposal* within that document (FDA, 2018b).

Barriers to harm reduction

Harm reduction strategies acknowledge that drug use may not immediately stop regardless of the treatment and prevention efforts and that although ending substance dependence is the goal, intermediate steps are required; in society, negative perceptions may result because of these misunderstandings (Bazazi, Zaller, Fu, & Rich, 2010). As a result of these social perceptions, it has been difficult to pass policy changes to protect those who are suffering from SUDs with the intermingled impacts of stigma. There is ongoing debate about whether medical care for opioid overdose should be in the hands of laypeople; however, research has suggested that laypeople are fully capable of initial response to an opioid overdose with basic training; furthermore, naloxone trainings and counseling points should emphasize that laypeople should initiate emergency medical care and stay with the patient until further care arrives. Lastly, there are some negative perceptions of the economic benefit to saving the lives of people with SUDs and the value that they can provide to society. If the opportunity to save their life does not exist, then they are never provided with the opportunity to seek treatment on their own terms.

THE PHARMACIST'S ROLE IN PUBLIC HEALTH TO REDUCE THE BURDEN FROM THE OPIOID CRISIS

The pharmacist's role in public health is expanding, with public health roles focused on the opioid crisis meeting an urgent need for communities and healthcare systems alike. Pharmacist clinical and public health roles in addressing the opioid crisis are expanding more quickly than can be captured by the literature.

Engaging with healthcare systems

Healthcare systems across the United States are working diligently to reduce the morbidity and mortality from the opioid crisis. Health system efforts, including the efforts of pharmacists, have focused on improving opioid prescribing (Cobaugh et al., 2014; Genord, Frost, & Eid, 2017; Tran et al., 2017), often concentrating on educating healthcare prescribers on opioid prescribing guidelines that provide nonopioid alternatives for pain relief and specific guidance on opioid prescriptions (Dowell, Haegerich, & Chou, 2016), as well as using pharmacists in recognizing and managing opioid toxicity (Cobaugh et al., 2014), and naloxone coprescribing (Duvivier et al., 2017; Wilson, Rodriguez, Carrington, & Fagan, 2017). Pharmacists working in healthcare systems or academic institutions may find opportunities to serve in a teaching role, providing education to prescribers on the guidelines and technical support in informatics solutions to encourage safe prescribing. Pharmacists across the nation are expanding opioid education and naloxone distribution out of various practices, including emergency rooms, community pharmacies, and ambulatory care (Lacroix, Thurgur, Orkin, Perry, & Stiell, 2018; Mueller, Walley, Calcaterra, Glanz, & Binswanger, 2015; Pauly, Vartan, & Brooks, 2018). Pharmacists also support healthcare systems in assessment of opioid-related risk, opioid dose management, and opioid-tapering clinical services (Jacobs et al., 2016; Norman et al., 2017).

The expanding role of the community pharmacist

Community pharmacists can play a critical role in overdose prevention and naloxone distribution (Morton et al., 2017; Mueller et al., 2015; Palmer, Hart, & Freeman, 2017). Community pharmacists may also contribute to abuse prevention by helping to detect fraudulent prescriptions, staying up to date with current guidelines, and being aware of new safety programs such as prescription drug monitoring programs (Nguyen, Chung, Osburn, Della Paolera, & Chavez, 2017). Community pharmacists may also find benefit in systems and protocols that help to communicate concerns about a patient's opioid taking with the patient and the prescriber (Rickles, Huang, Gunther, & Chan, 2018).

The provision of medication-assisted treatment

Pharmacists – particularly those practicing in rural and medically underserved areas – are well positioned to serve in clinical roles in the provision of MAT because of their advanced clinical training and accessibility. Pharmacy practice focused on MAT has progressed faster than is reflected in the literature, but the practice of clinical pharmacists practicing at Indian Health Service (IHS) locations in the Southwest, Midwest, and Great Lakes regions has been described in the literature (Duvivier et al., 2017). These pharmacists serve culturally diverse American Indian populations throughout the United States in novel practices that include pain management clinics and MAT programs; in this role, they interface with tribal and federal programs to affect the opioid epidemic in Indian Country. Pharmacists practicing in multidisciplinary teams and novel practices at IHSlocations have paved the way for contemporary pharmacy practice to reduce the morbidity and mortality from the opioid crisis.

Engaging with the community to address the opioid crisis

There are major needs for pharmacists to engage with community coalitions to address the opioid crisis. Opioid overdose trainings, which may be provided by pharmacists, are known to be effective in increasing knowledge and confidence related to opioid overdose situations (Ashrafioun, Gamble, Herrmann, & Baciewicz, 2016). In a community capacity, pharmacists may work to expand access to naloxone by educating healthcare providers and laypeople on the use of naloxone to reverse opioid overdose (Lewis, Vo, & Fishman, 2017). Pharmacists may also expand their public health role to include uniting with community coalitions to plan and speak at community forums to address the opioid crisis (Palombi et al., 2017), participating in professional initiatives that engage pharmacists in expanding roles in the opioid crisis, and working on local, statewide, and national task forces that strive to reduce the morbidity and mortality from the opioid crisis.

Drug courts

Drug courts are problem-solving courts, within the category of treatment court, that use a specialized model in which the judiciary, probation, law enforcement, prosecution, defense, social service, and treatment communities work together to help individuals with a SUD into long-term recovery (Marlowe, 2003). Although not a well-established practice, pharmacists can play a key clinical role in drug court in providing medication information, health coaching, and medication therapy management (Palombi & Koh-Knox, 2016) while allowing student pharmacists an opportunity to evaluate their attitudes toward SUDs (Palombi, Fike, Change, Stratton, & Koh-Knox, 2018).

CONCLUSION

Pharmacists can play an important role in clinical and public health engagement in the opioid crisis. This work is desperately needed as lives continue to be lost to this epidemic. Effective pharmacist interaction with patients at high risk of opioid overdose can allow for increased distribution of the drug naloxone, improved delivery of MAT, and expansion of harm reduction programs. The pharmacist can play a key role in public health to reduce the impact of the opioid crisis.

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Final Examination Questions

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91. According to the United Nations Office on Drugs and Crime (UNODC) World Drug Report 2017, approximately what percentage of the global adult population used drugs for nonmedical purposes at least once in 2015?
    a. 1%.
    b. 5%.
    c. 10%.
    d. 15%.

92. According to the UNODC, which class of drugs is considered the most harmful worldwide?
    a. Methamphetamines.
    b. Hallucinogens.
    c. Opioids.
    d. Tranquilizers.

93. According to a Substance Abuse and Mental Health Services Administration report, what proportion of individuals with a substance use disorder also had an alcohol use disorder in 2014?
    a. 1 in 9.
    b. 1 in 10.
    c. 1 in 11.
    d. 1 in 12.

94. Which of the following is true about opioid overdose in the United States?
    a. Drug overdose deaths doubled in the United States between 1999 and 2014.
    b. Rates of death for overdoses involving heroin and synthetic opioids other than methadone increased only among Whites.
    c. Women are more likely than men to die of an overdose.
    d. Emergency department visits for opioid overdoses rose 30% in all parts of the United States from July 2016 through September 2017.

95. Which of the following is true regarding the role of economic distress in the opioid crisis?
    a. Research examining the role of economic distress in impoverished communities that struggle with the opioid crisis – such as the Rust Belt and the Iron Range – is robust.
    b. Poverty and substance use problems have an antagonistic relationship.
    c. Medicaid recipients are at lower risk of overdose because of their increased contact with the healthcare system.
    d. People on Medicaid are more likely to be prescribed opioids, at higher doses, and for longer duration.

96. Which of the following is true regarding disparities in the impact of the opioid crisis?
    a. Advantages in healthcare access may have contributed to increased opioid prescribing and availability among African American patients.
    b. Research has shown that rural drug users have significantly higher odds of lifetime use of opioids.
    c. Research has shown that urban drug users have earlier ages of onset for use.
    d. Studies have shown that Asian Americans have disproportionately high rates of overdose.

97. Which of the following is true regarding the historical context of the opioid crisis?
    a. Several large governmental and nongovernmental agencies did not manage possible conflicts of interest, leading to public mistrust.
    b. The Star Ratings approach to assessing the quality of pain management led to a reduction in opioid prescriptions.
    c. Mismanaged conflicts of interest have not played a role in the opioid crisis to date.
    d. Recognition of pain as a fifth vital sign was essential to reducing opioid prescribing in primary-care settings.

98. A report published by the Institute of Medicine attributed the rise in chronic pain prevalence during the 1990s to:
    a. Greater patient expectations for pain relief.
    b. Pulmonary disorders of an aging population.
    c. Languishing as a result of injury and cancer.
    d. Longer time spent in the workforce.

99. Which of the following is true?
    a. Research has shown that one in five new heroin users started by misusing prescription painkillers.
    b. Opioids are generally preferred to black tar heroin because of the latter's high cost.
    c. Many heroin users reported switching from opioids to heroin because of heroin's lower cost.
    d. Many heroin users prefer to use opioids because of their greater availability.

100. Which of the following is true?
    a. Most pharmacists embrace harm reduction techniques, including naloxone distribution.
    b. Pharmacists must use the tools available to them to ensure that an opioid prescription is indicated, effective, and safe.
    c. It is not the pharmacist's responsibility to ensure that a prescription was written for a legitimate medical purpose.
    d. A decrease in opioid prescribing will end the opioid crisis in the United States.

101. Which receptor is most commonly associated with opioid use?
    a. Alpha receptor.
    b. Delta receptor.
    c. Kappa receptor.
    d. Mu receptor.

102. What are the three common classifications of opioids?
    a. Oral, transdermal, subcutaneous.
    b. Opium derivatives, semisynthetics, synthetics.
    c. Immediate release, long acting, continuous.
    d. Schedule II, Schedule III, Schedule IV.

103. Which of the following is considered a semisynthetic opioid?
    a. Opium.
    b. Morphine.
    c. Hydrocodone.
    d. Methadone.

104. Which of the following is considered a synthetic opioid?
    a. Fentanyl.
    b. Codeine.
    c. Oxycodone.
    d. Heroin.

105. Which of the following long-acting opioids should be avoided for the treatment of chronic pain because of its risk profile?
    a. Morphine.
    b. Methadone.
    c. Oxymorphone.
    d. Hydromorphone.

106. Which of the following is true when initiating opioid treatment for acute pain?
    a. Benzodiazepines should be offered concurrently to treat anxiety from acute pain.
    b. The patient should be given a long-acting opioid dosed every 12 hours, along with a short-acting opioid.
    c. The patient should be treated with the lowest effective dose of opioids.
    d. The patient should start with transdermal opioids before initiating oral therapies.

107. Which of the following is true regarding opioid tapering?
    a. Rapid tapers may be initiated in patients taking more than 90 morphine milligram equivalents (MME) of an opioid per day at a decrease of 25% to 50% until they reach a dosage of 60 to 80 MME per day.
    b. The faster the taper, the less likely the patient will experience opioid withdrawal symptoms.
    c. Patients being tapered off opioid medications must refrain from using nonopioid therapies until the taper is complete.
    d. Detoxification is never necessary for individuals taking high doses of opioids.

108. Which of the following is true regarding prescription drug monitoring programs (PDMPs)?
    a. Only prescribers, and not their delegates, are allowed to access PDMPs.
    b. Law enforcement is strictly prohibited from accessing PDMPs.
    c. Medical examiners and coroners are strictly prohibited from accessing PDMPs.
    d. Information collected for a PDMP is considered protected health information and should be treated as that, covered under the Health Insurance Portability and Accountability Act.

109. Which of the following is true regarding urine drug screening?
    a. Obtaining a urine drug screen before initiation of opioid therapy is recommended.
    b. Because the benefits of periodic drug screening are outweighed by the cost, periodic urine drug screening is not recommended.
    c. False positives are not possible with urine drug screens that test for the presence of opioids.
    d. Expected results of urine drug screens should not be discussed with patients or their family members.

110. Which of the following is true regarding benzodiazepines?
    a. If benzodiazepines and opioids are taken together and require discontinuation, it is best to start a taper of the benzodiazepine medication to discontinuation, followed by a slow taper of the opioid, to minimize the risk of respiratory depression and avoid symptoms of withdrawal from both classes of drugs.
    b. A patient taking opioids and benzodiazepines together may experience difficulty breathing, bradycardia, hypotension, sedation, coma, or even death.
    c. Benzodiazepines can be tapered more quickly than opioids without risk of withdrawal or harm.
    d. Benzodiazepines are a component of appropriate multimodal therapy for individuals with chronic pain.

111. Which of the following correctly describes addiction?
    a. Addiction is largely a moral failure, because addicted individuals chose a lifestyle of substance abuse.
    b. Addiction is a brain disease that affects multiple brain circuits, including those involved in motivation and reward, learning and memory, and inhibitory control over behavior.
    c. Addiction is only problematic in individuals with lower socioeconomic status and lower educational status.
    d. Genetic vulnerabilities have been proven not to exist in addiction science.

112. Which of the following is true regarding physiological changes to the brain caused by drugs?
    a. Drugs are known to normalize intracellular signaling cascades.
    b. Drugs are known to modulate the expression of genes through epigenetic modifications.
    c. Drugs are unable to modulate the expression of genes through RNA modification.
    d. Addiction is associated with long-lasting physiological changes to the brain.

113. Which of the following is true regarding opioids and brain function?
    a. Opioids affect dopamine neurotransmission in the nucleus accumbens.
    b. Opioids are known to increase the □-aminobutyric acid-based projections into the ventral tegmental area.
    c. Opioids and other drugs of abuse work by decreasing dopamine levels in the brain.
    d. Opioids have no demonstrated impact on emotional responses and anxiety in those who are addicted to them.

114. Which of the following is true?
    a. A markedly diminished effect with continued use of the same amount of an opioid is a sign of withdrawal.
    b. The withdrawal symptoms when opioids are not taken are minimal.
    c. Tolerance describes the phenomenon of individuals taking a closely related substance to avoid unpleasant symptoms.
    d. Tolerance may be defined as a need for markedly increased amounts of opioids to achieve a desired effect.

115. Which is true about opioid use disorder (OUD)?
    a. OUD is a diagnosis that was introduced before the *Diagnostic and Statistical Manual of Mental Disorders,* fifth edition *(DSM-5).*
    b. OUD combined two disorders, opioid dependence and opioid abuse, from the fourth edition of the *DSM.*
    c. The specific diagnosis of OUD should be used even if the drug being used is heroin.
    d. The diagnosis of OUD can be applied to someone who uses opioid drugs and has at least two symptoms within a 2-month period.

116. Which of the following correctly lists symptoms of OUD?
    a. Feeling depressed and anxious that one has taken opioids.
    b. Feeling euphoria from opioid taking.
    c. Craving opioids.
    d. Fearing opioids.

117. Which of the following is true about OUD?
    a. Individuals may experience physical tolerance and experience physical withdrawal symptoms from opioids, but not have OUD, if under medical supervision.
    b. The *DSM-5* recognizes that addictive disorders are primarily physical.
    c. An OUD diagnosis is applicable to a person who uses opioids and experiences at least 1 of the 11 symptoms in a 12-month period.
    d. OUD is classified as severe if the individual has 2 or 3 symptoms in a 12-month period.

118. Which of the following is true about opioid screening?
    a. Screening, Brief Intervention, and Referral to Treatment (SBIRT) asks "How many times in the past year have you used an illegal drug?"
    b. The Opioid Risk Tool calculates the factors that place individuals at greater risk of having a substance use disorder.
    c. The C in the CAGE questionnaire stands for Consider.
    d. SBIRT targets individuals with dependent substance use.

119. Which of the following is true about SBIRT?
    a. SBIRT does not use standard screening tools.
    b. The screening step involves a health professional engaging with a patient who shows risky substance use behaviors in a short conversation.
    c. SBIRT is a late intervention approach.
    d. SBIRT is evidence based.

120. Which of the following is true?
    a. Regardless of which tool is used, every pharmacy or medical practice should determine which screening tools to use and when, how, and by whom they will be administered.
    b. It is rare that a patient would screen positive using opioid screening tests, so determination of steps to take when a person screens positive is not the best use of healthcare resources.
    c. Standardized screening tools can only be used in an inpatient setting.
    d. It is important for healthcare providers to avoid engaging in conversation or offering feedback or advice during the SBIRT screening process.

121. Which of the following is the hallmark sign of opioid toxicity?
    a. Reduced gut motility.
    b. Tiny, pinpoint pupils.
    c. Respiratory depression.
    d. Restlessness.

122. For someone who is not sleeping, respiratory depression can be identified as a respiratory rate of:
    a. 12 breaths per minute or less.
    b. 18 breaths per minute or less.
    c. 24 breaths per minute or less.
    d. 30 breaths per minute or less.

123. The presence of choking or snoring sounds with opioid overdose is often referred to as:
    a. Sleep apnea.
    b. Nasal respiration.
    c. Opioid apnea.
    d. Biot's respiration.

124. The cold and clammy feeling of the skin during opioid overdose is because of:
    a. Peripheral vasoconstriction.
    b. Activation of the opioid receptors in the Edinger-Westphal nucleus.
    c. Activation of mu-opioid receptors in the gastrointestinal tract.
    d. Hyperventilation.

125. Which naloxone dosage form does not require assembly and has a voice that guides the naloxone injection process?
    a. Narcan.
    b. Evzio.
    c. Naloxone nasal spray.
    d. Naloxone intramuscular injection.

126. Which naloxone dosage form does not require assembly and is administered nasally?
    a. Narcan.
    b. Evzio.
    c. Naloxone nasal spray.
    d. Naloxone intramuscular injection.

127. Which naloxone dosage form is the least expensive?
    a. Narcan.
    b. Evzio.
    c. Naloxone nasal spray.
    d. Naloxone intramuscular injection.

128. Which of the following is true regarding supportive care during an opioid overdose?
    a. 911 must only be called if an individual remains unresponsive.
    b. 911 must only be called if an individual ingested a long-acting opioid.
    c. Opioid withdrawal can be life threatening.
    d. Rescue breaths should be started immediately upon recognition that someone is not breathing.

129. Which of the following is true regarding naloxone prescribing and dispensing laws?
    a. All 50 states and Washington, D.C., allow pharmacists to independently prescribe naloxone.
    b. A standing order for naloxone authorizes pharmacists to provide naloxone to any person whom the pharmacist thinks might benefit.
    c. Collaborative practice agreements can be statewide or between a pharmacist and a prescriber.
    d. Oregon is the only state where the legislature has directly authorized pharmacists to dispense or distribute naloxone without a patient-specific prescription.

130. Which of the following is true?
    a. Few states have enacted Good Samaritan laws to protect individuals who attempt to reverse an opioid overdose with naloxone.
    b. Tolerance is likely increased when substances are mixed.
    c. Snorting and injecting typically result in a lower risk of overdose.
    d. Liver and lung disease can increase a person's risk of fatal opioid overdose.

131. SBIRT is an evidence-based tool that stands for:
    a. Screening Best Practices for Individuals in Recovery and Treatment.
    b. See and Believe In Recovery and Treatment.
    c. Screening, Brief Intervention, and Referral to Treatment.
    d. Serious Beliefs In Resources and Treatment.

132. Which of the following is true about stigma?
    a. Stigma is partially to blame for only 10% of the 23 million Americans who meet criteria for a substance use disorder (SUD) accessing treatment each year.
    b. The recognition of addiction as a disease rather than a moral failure contributes to stigma.
    c. Healthcare providers rarely contribute to stigma.
    d. Using terms such as *dirty* and *clean* in discussions about SUDs help to eliminate stigma.

133. Which is true about the Substance Abuse and Mental Health Services Administration's National Helpline?
    a. This tool only helps to identify services based on particular types of care.
    b. This tool can find available treatment beds at any given time.
    c. This tool is available by calling 1-800-662-HELP (4357).
    d. This tool does not allow for the identification of services based on insurance type.

134. Which of the following is true about the use of methadone in medication-assisted treatment (MAT)?
    a. Methadone is typically dosed at a maximum of 80 mg daily in divided doses to start, and the dose can be slowly tapered to reduce symptoms of withdrawal.
    b. When tapering methadone therapy, dose adjustments should be reduced by about 20% every 5 to 10 days to prevent significant withdrawal.
    c. Maintenance methadone dosages typically range from 80 to 120 mg per day and are determined when opioid withdrawal is prevented for 24 hours.
    d. Methadone is a naturally occurring opioid agonist that is used for treatment of opioid use disorder (OUD) only in the detoxification phases of treatment.

135. Which of the following is true about the use of buprenorphine in MAT?
    a. Buprenorphine for OUD treatment is typically low dose and comes in few drug delivery formulations.
    b. Combination formulations with buprenorphine have a higher likelihood of respiratory depression and sedation.
    c. Buprenorphine must not be combined with naloxone.
    d. Buprenorphine is a mixed opiate agonist-antagonist agent with partial agonistic effects at the mu-opioid receptor and antagonist effects at the kappa-opioid receptor.

136. Which of the following is true about naltrexone?
    a. To receive intramuscular naltrexone treatment, patients must be abstinent from using opioids or alcohol for at least 2 weeks before beginning therapy.
    b. The generic oral formulation of naltrexone can be used for rapid opioid detoxification or withdrawal (with clonidine or buprenorphine).
    c. Naltrexone is a partial opioid agonist blocking the effects of opioids by competitively binding their receptors.
    d. The intramuscular naltrexone formulation is delivered as an immediate-release suspension for gluteal injection weekly.

137. Which of the following forms of harm reduction serve as tertiary prevention and emergency response?
    a. Naloxone distribution and syringe access.
    b. MAT and naloxone distribution.
    c. Syringe access and MAT.
    d. Drug court and MAT.

138. Which of the following is true about naloxone?
    a. Naloxone is an opioid agonist.
    b. Naloxone works by outcompeting opioids at the mu-opioid receptors – binding to those receptors and blocking them – to prevent the opioids from causing fatal respiratory depression.
    c. Naloxone can only be obtained with a prescription.
    d. Because naloxone destroys the opioid, there is no possibility of re-overdose.

139. Which of the following is true about safe medication disposal?
    a. The preferred route of disposal for medication is flushing it down the toilet.
    b. Commercial drug deactivation systems have not been invented yet.
    c. Because the environmental risk of opioids always outweighs the risk of keeping them in medicine cabinets, it is never advisable to discard of them in household trash or in the toilet.
    d. Permanent collection sites registered with the U.S. Drug Enforcement Administration can be located by calling 1-800-882-9539.

140. Which of the following is true about the pharmacist's role in the opioid crisis?
    a. Pharmacists are not trained to assist with the provision of MAT.
    b. Pharmacists are ill equipped to educate the community on harm reduction approaches, including naloxone distribution.
    c. The expertise of pharmacists is not appreciated or needed in community collaborations to address the opioid crisis.
    d. Pharmacists can play a key role in naloxone distribution, syringe access, and authorized takeback of unwanted pharmaceuticals.