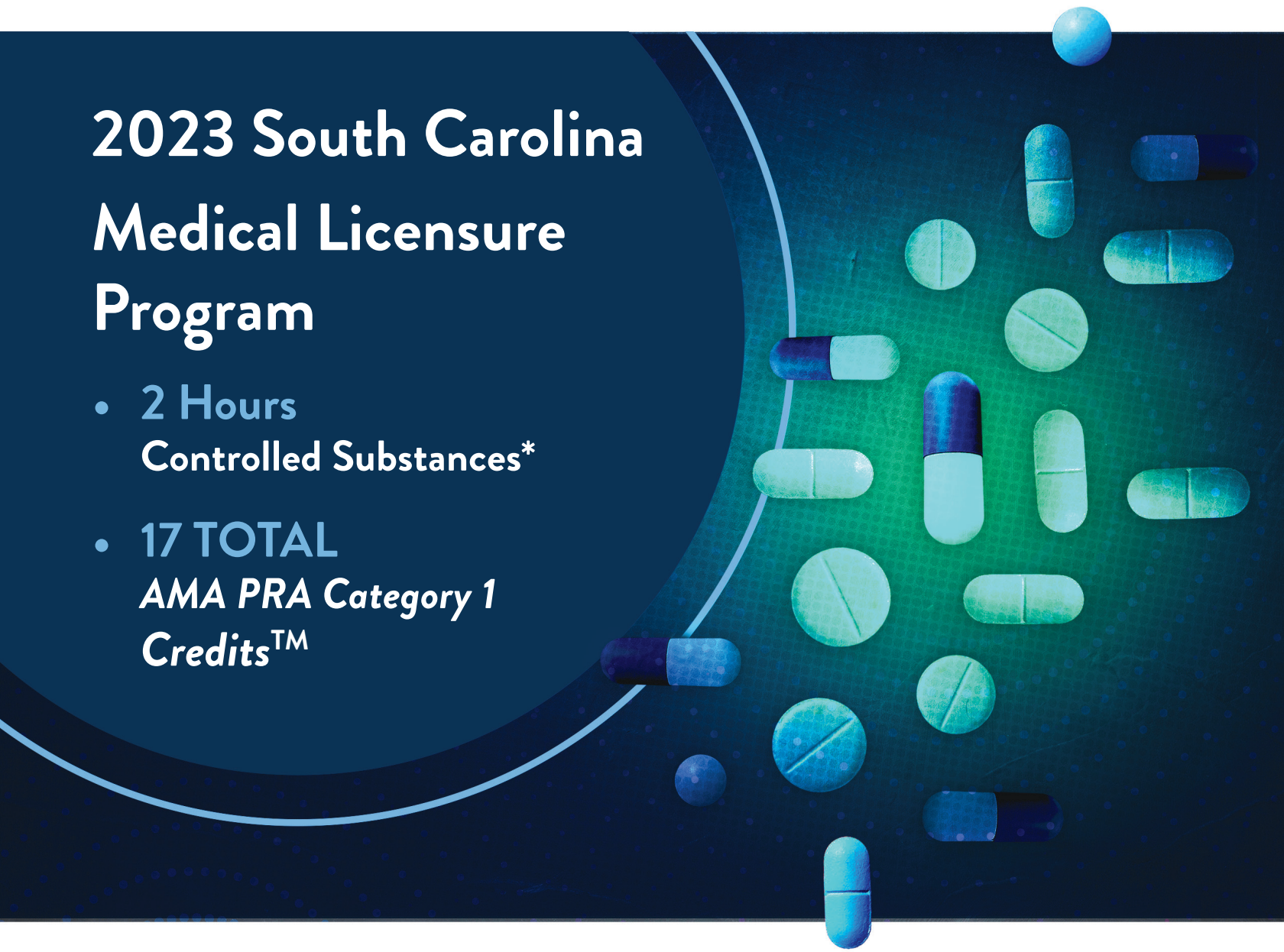
InforMed
Continuing Medical Education
By Colibri Healthcare

State Specific Continuing Medical Education

2023 South Carolina Medical Licensure Program



- **2 Hours**
  Controlled Substances*
- **17 TOTAL**
  AMA PRA Category 1 Credits™

ACCME ACCREDITED

*Physician CME Requirement:

2 Hours on prescribing & monitoring of controlled substances

CME FOR: *AMA PRA CATEGORY 1 CREDITS™* MIPS MOC STATE LICENSURE

SC.CME.EDU

CONTENTS

2023 SOUTH CAROLINA

***Completion of either Course One or Two fulfills the required two (2) hours on prescribing & monitoring of controlled substances for physicians (MD/DO) and podiatrists. Physician assistants with controlled substance prescriptive authority must complete both courses to satisfy the required four (4) hours on controlled substances.**

CME that counts for MOC

Participants can earn MOC points equivalent to the amount of CME credits claimed for designated activities (see page iii for further details). InforMed currently reports to the following specialty boards: the American Board of Internal Medicine (ABIM), the American Board of Anesthesiology (ABA), the American Board of Pediatrics (ABP), the American Board of Ophthalmology (ABO), the American Board of Otolaryngology–Head and Neck Surgery (ABOHNS), and the American Board of Pathology (ABPath). To be awarded MOC points, you must obtain a passing score, complete the corresponding activity evaluation, and provide required information necessary for reporting.

$75	$55	$50	$50
ENTIRE PROGRAM	COURSES 1 & 2	COURSE 1	COURSE 2

DATA REPORTING: Federal, State, and Regulatory Agencies require disclosure of data reporting to all course participants. InforMed abides by each entity's requirements for data reporting to attest compliance on your behalf. Reported data is governed by each entity's confidentiality policy. To report compliance on your behalf, it's mandatory that you must achieve a passing score and accurately fill out the learner information, activity and program evaluation, and the 90-day follow up survey. Failure to accurately provide this information may result in your data being non-reportable and subject to actions by these entities.

InforMed has joined the Elite Learning family

Two of the nation's top healthcare education providers have joined forces with one goal in mind: to offer physicians a state-of-the-art learning experience that fulfills your state requirements and empowers you with the knowledge you need to provide the best patient care.

Here's what you can expect from our new partnership:

- **COURSES:** In addition to the mandatory courses you need to renew your state license, you'll now have access to dozens of hours of elective courses and an expanded content library.
- **ACCOUNTS:** You'll also have access to a personalized learner account. In your account you can add, organize, and track your ongoing and completed courses. For instructions on how to set up your account, email us at office@elitelearning.com.
- **BOOK CODES:** You may notice a book code on the back cover of the latest InforMed program you've received in the mail. When entered on our new site, this code will take you directly to the corresponding self-assessment. See more information below.

How to complete

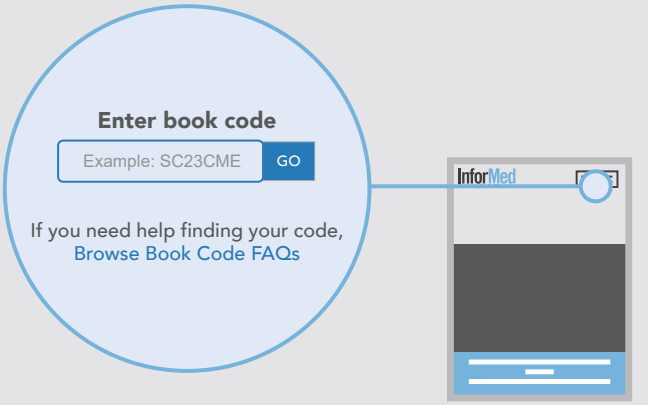
Please read these instructions before proceeding.

Read and study the enclosed courses and answer the self-assessment questions. To receive credit for your courses, you must provide your customer information and complete the mandatory evaluation. We offer three ways for you to complete. Choose an option below to receive credit and your certificate of completion.

Online

- Go to **BOOK.CME.EDU**. Locate the book code **SC23CME** found on the back of your book and enter it in the box then click **GO**. If you would like to choose a different program option, use the table below and enter the corresponding code in the box.
- If you already have an account created, sign in to your account with your username and password. If you do not have an account already created, you will need to create one now.
- Follow the online instructions to complete your self-assessment. Complete the purchase process to receive course credit and your certificate of completion. Please remember to complete the online evaluation.

Program Options	Code	Credits	Price
Entire Program	SC23CME	17	$75.00
Courses 1 & 2	SC23CME-55	5	$55.00
Course 1	SC23CME-501	2	$50.00
Course 2	SC23CME-502	3	$50.00



By mail

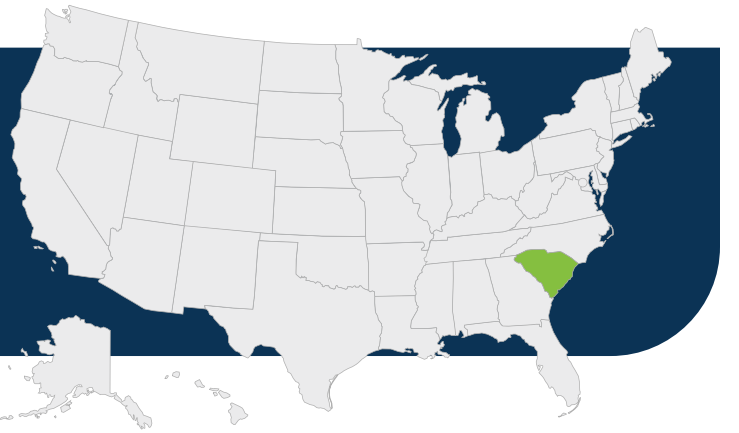
- Fill out the answer sheet and evaluation found in the back of this booklet. Please include a check or credit card information and e-mail address. Mail to **InforMed, PO Box 2595, Ormond Beach, FL 32175-2595**.
- Completions will be processed within 2 business days from the date it is received and certificates will be e-mailed to the address provided.
- Submissions without a valid e-mail will be mailed to the address provided.

By fax

- Fill out the answer sheet and evaluation found in the back of this booklet. Please include credit card information and email address. Fax to **1-800-647-1356**.
- All completions will be processed within 2 business days of receipt and certificates will be e-mailed to the address provided.
- Submissions without a valid e-mail will be mailed to the address provided.

BOOK.CME.EDU **BOOK CODE: SC23CME** **1-800-237-6999**

INFORMED TRACKS
WHAT YOU NEED,
WHEN YOU NEED IT



South Carolina Professional License Requirements

GENERAL CONTINUING MEDICAL EDUCATION REQUIREMENTS

PHYSICIANS (MD/DO), PHYSICIAN ASSISTANTS (PA), & PODIATRISTS (DPM)

Physicians (MD/DO) are required to complete forty (40) hours of continuing medical education prior to biennial license renewal. Thirty (30) of these hours must be in their specialty; ten (10) may be non-specialty. Physician assistants (PA) must maintain an active NCCPA certification. Podiatrists (DPM) must complete twenty-four (24) continuing education hours prior to biennial license renewal.

MANDATORY CONTINUING MEDICAL EDUCATION ON CONTROLLED SUBSTANCES

PHYSICIANS (MD/DO)

In compliance with §40-47-40 (2)(a), for biennial license renewal, physicians (MD/DO) must complete at least two (2) hours of CME related to approved procedures of prescribing and monitoring controlled substances listed in Schedules II, III, and IV of the schedules provided for in Sections 44-53-210, 44-53-230, 44-53-250, and 44-53-270, unless exempt.

PODIATRISTS (DPM)

In compliance with §40-51-140, for biennial license renewal, a podiatrist authorized pursuant to state and federal law to prescribe controlled substances is required to complete two (2) hours of continuing education related to approved procedures of prescribing and monitoring controlled substances listed in Schedules II, III, and IV of the schedules provided for in Sections 44-53-210, 44-53-230, and 44-53-250, unless exempt.

PHYSICIAN ASSISTANTS (PA) WITH CONTROLLED SUBSTANCE PRESCRIPTIVE AUTHORITY

In compliance with §40-47-965 (B)(3), for biennial license renewal, physician assistants with controlled substance prescriptive authority shall provide documentation of four (4) continuing education hours related to approved procedures of prescribing and monitoring controlled substances listed in Schedules II, III, and IV of the schedules provided for in Sections 44-53-210, 44-53-230, and 44-53-250, unless exempt.

We are a nationally accredited CME provider.
For all board-related inquiries please contact:

South Carolina State Board of Medical Examiners
110 Centerview Dr #202
Columbia, SC 29210
P: (803) 896-4500

COMPLETION DEADLINE:

MD/DO: 6/30/2023
DPM/PA: 12/31/2023

LICENSE/TYPES

MD/DO
DPM
PA

Disclaimer: The above information is provided by InforMed and is intended to summarize state CE/CME license requirements for informational purposes only. This is not intended as a comprehensive statement of the law on this topic, nor to be relied upon as authoritative. All information should be verified independently.

MOC/MIPS CREDIT INFORMATION

In addition to awarding *AMA PRA Category 1 Credits*™, the successful completion of enclosed activities may award the following MOC points and credit types. To be awarded MOC points, you must obtain a passing score and complete the corresponding activity evaluation.

Table 1. MOC Recognition Statements		
Successful completion of certain enclosed CME activities, which includes participation in the evaluation component, enables the participant to earn up to the amounts and credit types shown in Table 2 below. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting MOC credit.		
Board Programs		
MOCA®	**ABA**	American Board of Anesthesiology's redesigned Maintenance of Certification in Anesthesiology™ (MOCA®) program, known as MOCA 2.0®
ABIM CME MOC ACCREDITED	**ABIM**	American Board of Internal Medicine's Maintenance of Certification (MOC) program
	ABO	American Board of Ophthalmology's Maintenance of Certification (MOC) program
ABOHNS	**ABOHNS**	American Board of Otolaryngology – Head and Neck Surgery's Continuing Certification program (formerly known as MOC)
CME for ABPath CC	**ABPath**	American Board of Pathology's Continuing Certification Program
PART 2 MOC THE AMERICAN BOARD of PEDIATRICS	**ABP**	American Board of Pediatrics' Maintenance of Certification (MOC) program.

Table 2. Credits and Type Awarded							
Activity Title	***AMA PRA Category 1 Credits*™**	**ABA**	**ABIM**	**ABO**	**ABOHNS**	**ABPath**	**ABP**
Best Practices for Treating Pain with Opioid Analgesics	2 *AMA PRA Category 1 Credits*™	2 Credits LL	2 Credits MK	2 Credits LL & SA	2 Credits SA	2 Credits LL	2 Credits LL+SA
Evidence Based Guidance on Prescribing Controlled Substances	3 *AMA PRA Category 1 Credits*™	3 Credits LL	3 Credits MK	3 Credits LL & SA	3 Credits SA	3 Credits LL	3 Credits LL+SA
Existing and Emerging Patient Safety Practices	12 *AMA PRA Category 1 Credits*™	12 Credits LL & PS	12 Credits MK & PS	12 Credits LL, SA & PS	12 Credits SA & PS	12 Credits LL	12 Credits LL+SA
Legend: LL = Lifelong Learning, MK = Medical Knowledge, SA = Self-Assessment, LL+SA = Lifelong Learning & Self-Assessment, PS = Patient Safety							

Table 3. CME for MIPS Statement
Completion of each accredited CME activity meets the expectations of an Accredited Safety or Quality Improvement Program (IA PSPA_28) for the Merit-based Incentive Payment Program (MIPS). Participation in this Clinical Practice Improvement Activity (CPIA) is optional for eligible providers.

BEST PRACTICES FOR TREATING PAIN WITH OPIOID ANALGESICS

COURSE DATES:	MAXIMUM CREDITS:	FORMAT:
Release Date: 10/2021 Exp. Date: 9/2024	*2 AMA PRA Category 1 Credits*™	Enduring Material (Self Study)

TARGET AUDIENCE

All health care professionals who participate in the management of patients with pain.

HOW TO RECEIVE CREDIT:

- Read the course materials.
- Complete the self-assessment questions at the end. A score of 70% is required.
- Return your customer information/ answer sheet, evaluation, and payment to InforMed by mail, phone, fax or complete online at program website.

COURSE OBJECTIVE

To provide the fundamentals of acute and chronic pain management and a contextual framework for the safer prescribing of opioid analgesics that includes consideration of a full complement of non-opioid treatment options.

LEARNING OBJECTIVES

Completion of this course will better enable the course participant to:

1. Discuss pain and comorbidity assessments as appropriate to the individual patient and pain type and duration.
2. Discuss an individualized treatment plan utilizing or considering a full range of medication and non-medication options.
3. Identify risk or presence of OUD before initiating or continuing opioid therapy for pain.
4. Recognize signs and symptoms of OUD, strategies for optimal management, and when to refer to a specialist.

ACCREDITATION STATEMENT

InforMed is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

DESIGNATION STATEMENT

InforMed designates this enduring material for a maximum of 2 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

FACULTY

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DISCLOSURE OF INTEREST

In accordance with the ACCME Standards for Commercial Support of CME, InforMed implemented mechanisms, prior to the planning and implementation of this CME activity, to identify and resolve conflicts of interest for all individuals in a position to control content of this CME activity.

COURSE SATISFIES

2

PRESCRIBING & MONITORING OF CONTROLLED SUBSTANCES

SPECIAL DESIGNATION

This course satisfies two (2) hours on prescribing and monitoring of controlled substances.

The South Carolina Board of Medical Examiners requires physicians (MD/DO) to complete two (2) hours on safe prescribing and monitoring of controlled substances as a condition of renewal. Physician assistants with controlled substance prescriptive authority must complete four (4) hours on safe prescribing and monitoring of controlled substances as a condition of renewal. The South Carolina Board of Podiatry Examiners requires podiatrists authorized to prescribe controlled substances to complete two (2) hours on safe prescribing and monitoring of controlled substances as a condition of renewal.

FACULTY/PLANNING COMMITTEE DISCLOSURE

The following faculty and/or planning committee members have indicated they have no relationship(s) with industry to disclose relative to the content of this CME activity:

- Beth Dove
- Michael Brooks

The following faculty and/or planning committee members have indicated they have relationship(s) with industry to disclose:

- Melissa B. Weimer, DO, MCR, FASAM has received honoraria from Path CCM, Inc. and CVS Health.

STAFF AND CONTENT REVIEWERS

InforMed staff, input committee and all content validation reviewers involved with this activity have reported no relevant financial relationships with commercial interests.

DISCLAIMER

The Challenge of Treating Pain

The experience of pain brings great physical and emotional suffering as well as significant societal costs. Some 50 million U.S. adults live with chronic daily pain, and 19.6 million experience high-impact pain that interferes with daily life and work.[1] Pain is even more common in military veterans, particularly those who have served in recent conflicts: 66% reported pain in the previous three months, and 9% had the most severe pain.[2] The national cost of pain is estimated at between $560 billion and $635 billion annually.[1]

Pain that is unremitting and without adequate treatment can lead to a multitude of problems for the person who suffers, including anxiety, depression, disability, unemployment, and lost income.[1] Certain populations are more vulnerable than others to developing more severe chronic pain and disability, including women, older adults, and individuals from minoritized racial and ethnic backgrounds,[3] who are also at risk for having their pain undertreated.[3] People who lack access to optimal pain care experience more complications in medical and psychiatric conditions.[1] Failure to give adequate care for pain from injury or surgery can prolong recovery times, leading to hospital readmissions and transition to chronic pain.[1]

The challenge of managing acute and chronic pain is complicated by an ongoing public health crisis related to opioid overdose, a category that includes prescription opioids, heroin, and illicitly-produced fentanyl and its analogues.[4] Numerous families have endured tragedy in the form of opioid-related overdose deaths, which doubled from more than 21,000 in 2010 to more than 42,000 in 2016.[4] As of 2019, of the approximately 71,000 drug-related overdose deaths in the United States, close to 50,000 of them involved opioids, more than 14,000 of which involved prescription opioids (Figure 1).[5] Over the past decade, the fatalities have been strongly driven by a proliferation of illicitly-produced high-potency synthetic opioids, but prescription opioids and other sedating medications, particularly benzodiazepines, also contributed to fatal overdoses.[6] In all, more than 136 Americans die every day from overdoses that involve a prescription or illicit opioid. Moreover, overdose deaths spiked during the COVID-19 pandemic, particularly deaths involving synthetic opioids.[7]

These grim statistics illustrate how important it is to keep potential public health consequences in mind when prescribing any type of controlled substance, including opioids. The economic burden of opioid misuse reaches $78.5 billion a year in healthcare, lost productivity, addiction treatment, and criminal justice costs.[8] As of 2018, more than 2 million Americans had an opioid-use disorder (OUD) involving prescription or illicit opioids. Of people age 12 or older in 2019, there were:[4]

- 1.6 million new individuals who misuse prescription pain relievers
- 949,000 new individuals who misuse prescription sedative-hypnotics
- 901,000 new individuals who misuse prescription stimulants

Many people who misuse opioids are not receiving regular medical care or prescribed opioids. Indeed, most people who are prescribed opioids for pain treatment do not misuse their medications. However, roughly 21% to 29% of patients prescribed opioids for chronic pain do misuse them, and between 8% and 12% of them develop an OUD.[9] Furthermore, an estimated 4% to 6% of people who misuse prescription opioids transition to non-prescribed opioid and/or illicit opioid use.[10-12] Approximately 75% to 80% of people who use heroin misused prescription opioids first.[10,11]

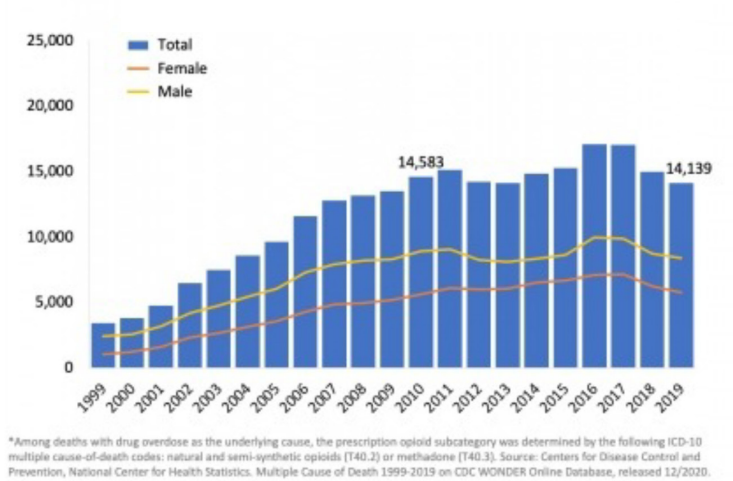
Health care practitioners (HCPs) play a key role in facilitating appropriate use of opioids and other sedating medications when prescribed for acute and chronic pain. Pain care is most effective when it combines multiple disciplines and utilizes a broad range of evidence-based pharmacologic and nonpharmacologic treatment options.[13,14] Opioids are associated with small improvements in pain and function versus placebo when used up to six months; however, evidence of longer-term effectiveness is limited, whereas increased harms from use beyond six months appear to be dose dependent.[4] Moreover, non-opioid options may bring equivalent or better patient outcomes with less risk: a comparative effectiveness review of evidence performed by the Agency for Healthcare Research and Quality found no difference in improvement in pain, function, mental health status, sleep, or depression when opioids versus non-opioid medications were used up to six months.[4]

At the same time, there is a recently recognized potential for harm in suddenly discontinuing or rapidly tapering doses in patients who have been on long-term opioids or in forcing patients who have been stable on higher doses to reduce to a set threshold dose.[1,15-17] It is also critical that HCPs recognize and optimally manage OUD when present. Distressingly few people who need treatment for substance-use disorder (SUD) are able to access it, and far more people need treatment for OUD than receive it. In 2012, the treatment gap was nearly a million people, with about 80% of opioid treatment programs nationally operating at 80% capacity or greater.[18] Solutions will include more accessibility of OUD treatment, including greater access to medications to treat OUD, and measures to prevent prescription and illicit drug misuse from developing in the first place.[19]

For acute pain and for some chronic pain, unresponsive to non-opioid therapies, opioids may form part of a customized treatment plan. A subset of patients may benefit from treatment with opioids long term, for example, during severe exacerbations of pain during the course of chronic conditions.[20] More than ever, HCPs are called on to optimize a range of available therapies and reserve opioids for when the benefits are expected to outweigh the risks and non-opioid options are inadequate.

This educational activity is built on core messages of the U.S. Food and Drug Administration's (FDA's) Blueprint for the Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS). It provides guidance on safely prescribing opioid analgesics, including all extended-release and long-acting (ER/LA) and immediate-release/short-acting (IR/SA) formulations. It is targeted to all HCPs who treat and monitor patients with pain, not prescribers alone. It stresses the importance of competence in considering and using a broad range of pharmacologic and nonpharmacologic therapeutic options for managing pain as well as in recognizing and managing OUD when indicated. The goal is to equip HCPs to recognize and manage any adverse events that may arise when a trial of potentially long-term opioids is part of a comprehensive treatment plan.

Figure 1. National Drug Overdose Deaths Involving Prescription Opioids* Among All Ages, 1999-2019[5]



*Among deaths with drug overdose as the underlying cause, the prescription opioid subcategory was determined by the following ICD-10 multiple cause-of-death codes: natural and semi-synthetic opioids (T40.2) or methadone (T40.3). Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2019 on CDC WONDER Online Database, released 12/2020.

Pain Definitions

The International Association for the Study of Pain (IASP) revised its pain definition in 2020 to better convey pain's nuances and complexities and to improve its assessment and management. The IASP defines pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage."[21] The IASP further describes pain as follows:[21]

- As a personal experience that is influenced to varying degrees by biological, psychological, and social factors
- As a separate phenomenon from nociception that cannot be inferred solely from activity in sensory neurons
- As a concept learned through the life experiences of individuals
- As an experience that should be respected
- As serving an adaptive role that may, nonetheless, have adverse effects on function and social and psychological well-being
- As existing independently of the ability to express its presence verbally, i.e., verbal description is only one of several behaviors to express pain, and inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain

There are no precise clinical markers for pain, which is experienced by the individual as a constellation of biological, psychological, and social factors that include race and ethnicity (Figure 2).[1] This biopsychosocial model is now preferred to an earlier era's biomedical model of pain care, which primarily aimed medical, procedural, and surgical treatments at a presumed biological pain generator in an attempt to fix or numb pain.[20] Given pain's complexity, it is important to perform a thorough patient evaluation so that the presumed or differential diagnosis is accurate in order to select the best therapeutic option.[1]

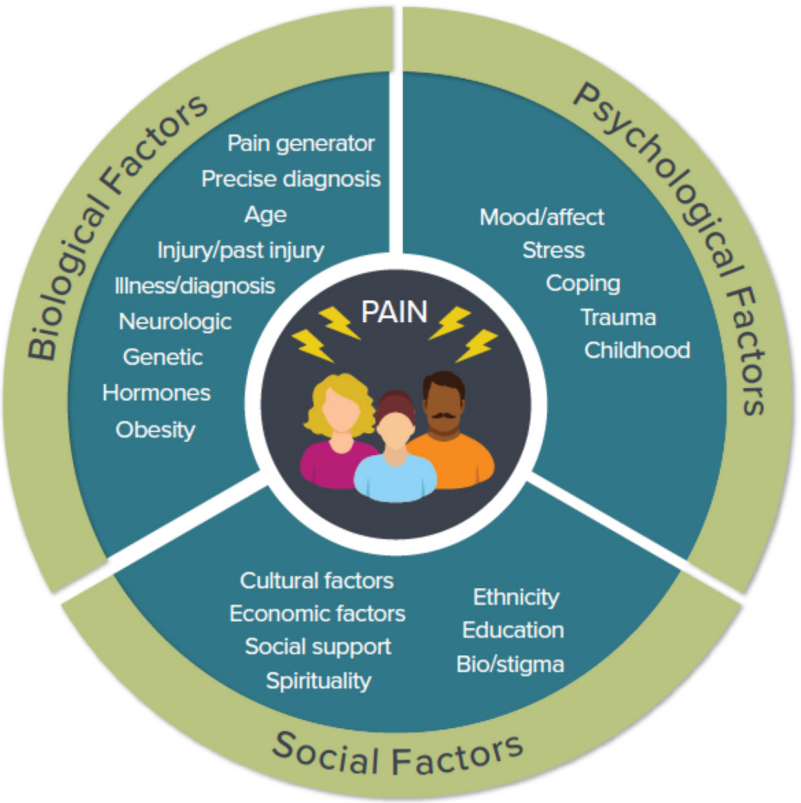
Pain is protective and essential for survival when understood as a warning signal that something has gone wrong in the body. However, when pain persists indefinitely the central nervous system (CNS) begins to sense, transmit, modulate, and interpret the pain experience differently.[14] When the nociceptors, or sensory receptors, become sensitized, they discharge more frequently. In peripheral sensitization, this state of heightened neuron excitability occurs at the site where the pain impulse originated in the body; in central sensitization, it occurs in the spinal neurons, which begin to fire spontaneously, resulting in pain that intensifies and lasts far longer than the stimulus applied.[14] Sensitization can result in hyperalgesia, where response to pain-causing stimuli is intensified, and allodynia, a pain response to stimuli that normally are not painful.[14] Therefore, the resulting pain comes not just from an injury site but from neural impulses. The pathologies created by central sensitization can persist and continue to generate pain impulses indefinitely, far outlasting pain's usefulness as a warning signal.

Pain Classifications

Pain can be categorized in several ways, including by type, duration, etiology, and pathophysiology.

- Acute pain is a physiologic response to noxious stimuli with a sudden onset and expected short duration.[1] It commonly occurs as a result of burn, trauma, musculoskeletal and neural injury, and after surgery or other procedures in the perioperative period.[1,20] Acute pain flares may also occur periodically in the course of chronic pain and medical conditions.[1] Anxiety and distress may exacerbate the acute pain experience.[22]
- Chronic pain lasts longer than normal healing and is generally diagnosed after persisting or recurring for longer than three-to-six months.[14]
  - Chronic pain's many possible causes include injuries, malignancies, chronic diseases, medical treatments or surgeries, or inflammation that appears as a result of injury or chronic disease.
  - Chronic pain may occur in the absence of a defined injury or cause.
  - Anxiety, depression, and stress are known to complicate the chronic pain experience.[1]
  - Chronic relapsing pain conditions have periods of remission and frequent relapses (e.g., various degenerative, inflammatory, immune-mediated, rheumatologic, and neurologic conditions such as multiple sclerosis [MS], trigeminal neuralgia, Parkinson's disease, complex regional pain syndrome [CRPS], porphyria, systemic lupus erythematosus, lumbar radicular pain, migraines, and cluster headaches).[1]
- Nociceptive pain is the normal response to any type of stimulus that results in tissue damage and includes visceral and somatic pain.[14] Examples of nociceptive or inflammatory pain include postoperative pain, osteoarthritis, mechanical low back pain, sickle cell crises, and pain from traumatic injuries.
  - Visceral pain is nociceptive pain that arises from the body's organs and may be cramping, throbbing, and/or vague.[14] Examples are pain related to myocardial infarction, pancreatitis, or cholecystitis.
  - Somatic pain, whether superficial or deep, is nociceptive pain that results from issues within the body's bone, joints, muscles, skin, or connective tissue; it may be localized and stabbing, aching, and/or throbbing.[14] Examples include mechanical low back pain, osteoarthritis, and muscle sprain or strain.
- Neuropathic pain results from damage to or abnormal processing of the CNS or peripheral nervous system and may be sharp, stabbing, burning, tingling, and/or numb.[14] Certain neuropathic pain conditions may be diagnosed as chronic pain before the three-month mark.[23] Examples include diabetic neuropathy, regional pain syndrome, or trigeminal neuralgia.

Figure 2. The Biopsychosocial Model of Pain[1]



- Referred pain spreads beyond the initial injury site and can have both nociceptive and neuropathic features.[14]
- Chronic pain may be primarily nociceptive or neuropathic, or have mixed nociceptive-neuropathic characteristics.

New Diagnostic Categories for Chronic Pain

Accurately diagnosing a pain condition can be challenging, particularly when the etiology or pathophysiology of the pain is not clearly understood. To systematically gather together all relevant codes for the management of chronic pain, new diagnostic categories in the International Statistical Classification of Diseases and Related Health Problems (ICD-11) take effect in January 2022.[24] These diagnostic categories are intended to assist HCPs in reaching an accurate diagnosis to better create an optimal treatment plan.

Per ICD-11, chronic pain is considered primary when pain has persisted for more than three months, is associated with significant emotional distress and/or functional disability, and is not better accounted for by another condition. Thus, in chronic primary pain, the pain is the chief complaint and disease in itself. A diagnosis of somatic symptom disorder, is not made on the basis of unexplained pain alone but requires positive psychiatric criteria. The six subgroups of chronic primary pain are:[24]

- Chronic primary pain
- Chronic widespread pain (e.g., fibromyalgia)
- Chronic primary visceral pain (e.g., irritable bowel syndrome)
- Chronic primary musculoskeletal pain (e.g., nonspecific low-back pain)
- Chronic primary headache or orofacial pain (e.g., migraine, tension-type headache, trigeminal autonomic cephalalgias)
- Chronic regional pain syndrome

Chronic pain is secondary when it may, at least initially, be a symptom of an underlying disease. A diagnosis may be made independent of biological or psychological contributors, unless another diagnosis better fits the symptoms. The six subgroups of chronic secondary pain are:

- Chronic cancer-related pain
- Chronic neuropathic pain
- Chronic secondary visceral pain
- Chronic posttraumatic and postsurgical pain
- Chronic secondary headache and orofacial pain
- Chronic secondary musculoskeletal pain

Chronic neuropathic pain is further subdivided by whether its origin is peripheral or central.[23] Peripheral neuropathic pain is caused by a lesion or disease of the peripheral somatosensory nervous and includes:[23]

- Trigeminal neuralgia is an orofacial pain condition of the trigeminal nerve with shooting, stabbing, or electric-shock-like pain that starts and ceases abruptly, and is triggered by innocuous stimuli.
- Chronic neuropathic pain after peripheral nerve injury is caused by a peripheral nerve lesion with history of nerve trauma, pain onset in temporal relation to the trauma, and pain distribution within the innervation territory.
- Painful polyneuropathy is caused by metabolic, autoimmune, familial, or infectious diseases, exposure to environmental or occupational toxins, or treatment with a neurotoxic drug (as in cancer treatment), or can be of unknown etiology.
- Postherpetic neuralgia is pain persisting for more than three months after the onset or healing of herpes zoster.
- Painful radiculopathy stems from a lesion or disease involving the cervical, thoracic, lumbar spine, or sacral nerve roots, commonly caused by degenerative spinal changes but also by numerous other injuries, infections, surgeries, procedures, or diseases.
- Other, not covered by above codes, includes carpal tunnel syndrome and disorders for which information is still insufficient to assign a precise diagnosis.

Central neuropathic pain is caused by a lesion or disease of the central somatosensory nervous system, and the pain may be spontaneous or evoked.[23] Central neuropathic pain conditions include:[23]

- Chronic central neuropathic pain associated with spinal cord injury
- Chronic central neuropathic pain associated with brain injury
- Chronic central post-stroke pain
- Chronic central neuropathic pain caused by MS
- Other, specified and unspecified

Conditions may be referenced under more than one category as with chronic painful chemotherapy-induced polyneuropathy, classed as cancer-related pain (by etiology) and also as neuropathic pain (by nature).

Although it is clinically useful to speak of chronic pain, it is important to remember that pain is a dynamic experience whose onset, maintenance, and exacerbation is not confined to set temporal categories.[25] Thus, patients who experience significant pain that lasts beyond typical healing periods or the three-month diagnostic period for chronic pain may improve with conservative measures. Conversely, some types of neuropathic pain or sudden onset pain from injury or disease does not require three months before treating the condition as chronic as the pain is likely to persist or recur indefinitely.[23] Because pain can be both a symptom and a disease, an accurate diagnosis is vital to treating the biologic source of pain when it is known and to expediting timely management of pain of uncertain origin.[25] All subtypes of chronic pain should be understood to have multiple biological, psychological, and social factors that contribute to the individual's pain experience, in keeping with the biopsychosocial framework.

Barriers to Effective Pain Care

The multimodal, multidisciplinary treatment approach is recognized as optimal for pain care; nevertheless, barriers to accessing this type of care for patients are numerous and entrenched in the health-care delivery system. It should be fully recognized that HCPs are asked to provide optimal pain care and lessen the risks from opioids in an environment that frequently provides inadequate support for practitioners and scant access for patients. A task force of health care associations convened by the American Medical Association to study and make recommendations to improve patient pain care described evidence-based care as "ensuring patients have access to the right treatment at the right time without administrative barriers or delay."[26]

Insurance barriers to providing optimal patient care are present in the policies of public and private payers and pharmacy chains as well as pharmacy benefits managers. These barriers include delays and denials from prior authorization, step therapy, treatment quantity limits, high cost-sharing, coverage limits and restrictive access for non-opioid and nonpharmacologic treatments for pain, and strict opioid limits enforced without regard to individual patient need.[26]

Barriers to the provision of nonpharmacologic therapies in particular include coverage that is absent or inadequate, unreceptive attitudes of HCPs and patients, and shortages of pain and behavioral health care specialists.[27]

An Inter-agency Task Force convened by the Department of Health and Human Services (HHS) to recommend best practices in pain care proposed several ways of addressing gaps:[1]

- Create clinical practice guidelines to better incorporate evidence-based complementary and integrative therapies into practice.
- Improve insurance coverage and payment for different modalities on the basis of the best practices identified in new guidelines.
- Improve coverage and payment for multidisciplinary team care coordination.
- Expand access to treatment and geographical coverage via the use of telemedicine and other technological delivery methods for psychological and behavioral health interventions.
- Increase the number and training of qualified practitioners in behavioral health and other evidence-based complementary and integrative disciplines.
- Provide better education as well as time and financial support for primary care practitioners who give patients the sole available pain care in many parts of the country.

Another barrier to pain care is the stigma in living with chronic pain, which is often cited by patients and their caregivers as a difficulty worsened by lack of objective biomarkers for pain, the invisible nature of the disease, and societal attitudes that equate acknowledging pain with weakness.[28] Compassion, empathy, and trust within a practitioner-patient relationship are key to navigating these challenges. It can help to offer education to the patient regarding the underlying disease processes of pain and to encourage them to seek help early for pain that persists beyond the expected time frame. When opioids are indicated, it is strategic to counsel patients that opioids are an appropriate part of their pain treatment plan so that the stigma of the societal opioid crisis does not interfere with appropriate treatment and good outcomes for the patient regarding opioid use.[20]

Treatment Options for Managing Pain

The HHS Inter-Agency Task Force on best practices in pain management categorizes options for pain treatment as medication, restorative, interventional, behavioral health, and complementary and integrative.[1] Medications include opioid and non-opioid pharmacologic treatments. What follows are examples of each (not an exhaustive list) and a brief discussion of the evidence base underpinning these options.

Nonpharmacologic Options for Pain

A number of evidence-based nonpharmacologic treatments are recommended, either used alone or in combination with other modalities within a treatment plan that is individualized and draws from multiple disciplines (Table 1).[1,29,30] Nonpharmacologic options should not be considered "alternatives" to opioids but are encouraged as part of a comprehensive pain plan in keeping with the evidence base, patient access to competent practitioners, and adequate insurance coverage and reimbursement.

Frequently covered modalities for chronic pain include cognitive behavioral therapy (CBT), physical therapy, certain injections, exercise, and electrical stimulation.[29] Patients may find it helpful to combine approaches that include nutritional support, healthy lifestyle changes, patient education, sleep hygiene instruction, and relaxation and visualization techniques. The noninvasive nature and low side effect profile of nonpharmacologic treatments suggest they should be used first and preferentially.

Restorative Therapies

Physical and occupational therapy are recommended for acute and chronic pain and are best combined as part of a multidisciplinary treatment plan after a thorough assessment.[1] Traction is frequently used as part of physical therapy and, although evidence that it is clinically effective is lacking, the HHS Inter-Agency Task Force suggests it should be investigated separately and considered as a treatment modality for low-back or neck pain.[1] Unfortunately, despite evidence of improved outcomes, use of these physical and occupational therapies is frequently challenged by incomplete or inconsistent reimbursement policies, and policymakers have been asked to look more closely at improving payer polices.[1]

There is high-quality evidence that therapeutic exercise improves outcomes over bed rest.[1] Principally investigated as a treatment for spinal pain, therapeutic exercise has been shown help patients function better and to help them overcome the anxiety and fear of movement that worsen pain and disability.

Transcutaneous electric nerve stimulation research is plagued by a lack of high-quality, unbiased studies, and overall evidence of efficacy is limited.[1] It has been investigated for treatment of acute low-back pain, postpartum pain, phantom limb pain, and knee osteoarthritis, and, despite limited evidence, can be considered among the safer self-care options with appropriate patient education.[1]

Massage therapy includes Swedish, shiatsu, and deep tissue or myofascial release types. A systematic review found massage can be effective in the general population for pain, anxiety, and to improve health-related quality of life compared to sham, no treatment, and active comparators.[31]

The application of cold and heat is a standard approach in relieving the symptoms of acute pain. Evidence supports use of cold therapy to reduce pain after surgery and heat wraps to relieve pain symptoms and increase function in acute low-back pain.[1]

The evidence has not been robust that therapeutic ultrasound is more effective than placebo for musculoskeletal pain conditions; however, recent findings show it can be effective in relieving knee osteoarthritis.[1] Nonrigid bracing may improve function and is unlikely to cause muscle atrophy when used for short periods.[1]

Interventional Options

Interventional pain management describes a variety of techniques that vary in terms of their invasiveness. Techniques may use image-guided technology to help diagnose and treat sources of acute and chronic pain. Such treatments may help minimize the use of oral pain medication, including opioids, but have risks as well as advantages that should be understood and discussed with patients. Low complexity interventions include:

- Trigger point injections, usually composed of an anesthetic like lidocaine, disrupt the tense bands of skeletal muscle fibers that produce pain and can be used to treat headaches, myofascial pain syndrome, and low-back pain.[1]
- Joint injections, often of corticosteroid into various joints, which are useful for inflammatory arthritis and basal joint arthritis.[1]
- Peripheral nerve injections, which are injections of local anesthetic agents or other medications by single injection or continuously by catheter, frequently delivered perioperatively and also useful for treatment or prevention of peripheral neuropathies, nerve entrapments, CRPS, headaches, pelvic pain, and sciatica.[1]

Medium complexity interventions include:

- Facet joint nerve blocks as common diagnostic and therapeutic treatments for facet-related spinal pain of the low back and neck.[1]
- Epidural steroid injections to deliver anti-inflammatory medicine to the epidural space, which are frequent treatments for back and radicular pain and have been shown to reduce need for health care visits and surgeries, although risks should be weighed and discussed with the patient.[1]
- Radio-frequency ablation, which uses needles to deliver high-voltage bursts of energy near nerves to block pain transmission and has shown promise for cervical radicular pain.[1]
- Regenerative/adult autologous stem cell therapy, which is a promising area of research for many painful conditions.[1]

Table 1. Noninvasive, Nonpharmacologic Approaches to Pain Management[1]

Restorative	Behavioral Health	Complementary and Integrative
• Physical therapy • Occupational therapy • Physiotherapy • Therapeutic exercise • Transcutaneous electric nerve stimulation • Massage therapy • Traction • Cold and heat • Therapeutic ultrasound • Bracing • Chiropracty	• Cognitive behavioral therapy • Acceptance and commitment therapy • Mindfulness-based stress reduction • Emotional awareness and expression therapy • Self-regulatory/psychophysiological approaches: ° Biofeedback ° Relaxation training ° Hypnotherapy	• Acupuncture • Massage, manipulative therapies • Mindfulness-based stress reduction • Spirituality • Tai chi • Yoga • Reiki

- Cryoneuroablation, which uses a cryoprobe to freeze sensory nerves at the source of pain to provide long-term pain relief and may be considered for numerous intractable pain conditions that include paroxysmal trigeminal neuralgia, chest wall pain, phantom limb pain, neuroma, peripheral neuropathy, knee osteoarthritis, and neuropathic pain caused by herpes zoster.[1]
- Neuromodulation, which delivers stimulation to central or peripheral nervous system tissue and has shown efficacy in low-back and various headache disorders.[1]

High complexity interventions include:

- Spinal cord stimulators, which are devices to deliver a form of neuromodulation that has demonstrated efficacy in low-back and lower extremity pain[1]
- Intrathecal pain pumps, which can deliver opioids (and other medications) into the spinal fluid with fewer side effects and at lower doses than with oral opioids, although significant side effects such as delayed respiratory depression, granuloma formation, and opioid-induced hypogonadism can occur.[1]
- Vertebral augmentation, which uses various techniques, including injecting cement into vertebral compression fractures that are painful and refractory to treatment.[1]
- Interspinous process spacer devices, which can provide relief for patients with lumbar spinal stenosis with neuroclaudication.[1]

Behavioral Health Options

There is ample evidence that chronic pain is both associated with and complicated by psychiatric, psychological, and social factors that exert tremendous influence over the pain experience and the success of treatment.[32-34] The higher the impact of pain, the worse the disruption to the person's relationships, work, physical activity, sleep, self-care, and self-esteem.[1] Those with comorbidities that include depressive and anxiety disorders face additional challenges that complicate treatment by worsening pain and quality of life and rendering the activities of daily living more difficult. An estimated 30% of patients with chronic pain also have an anxiety disorder, such as generalized anxiety disorder, panic disorder, post-traumatic stress disorder (PTSD), and agoraphobia.[1]

Furthermore, high levels of depression and anxiety worsen pain and pain-related disability.[35] Patients with chronic pain have more disability than patients with other chronic health conditions.[1] In addition, patients with chronic pain are at increased risk for psychological distress, maladaptive coping, and physical inactivity related to fear of reinjury.[32] Behavioral therapies are valuable for helping patients cope with the psychological, cognitive, emotional, behavioral, and social aspects of pain.

Common behavioral health approaches include:

- Behavioral therapy for pain, which seeks to reduce maladaptive pain behaviors, such as fear avoidance, and increase adaptive behaviors with the goal of increasing function; it has demonstrated effectiveness (and cost-effectiveness) for reducing pain behaviors and distress and improving overall function.[1]
- CBT, which focuses on shifting cognitions and improving pain coping skills in addition to altering behavioral responses to pain; CBT is effective for a variety of pain problems (including low-back pain and fibromyalgia), helps improve self-efficacy, reduces pain catastrophizing, and improves overall functioning.[1,30,36]
- Acceptance and Commitment Therapy, which emphasizes observing and accepting thoughts and feelings, living in the present moment, and behaving according to one's values; it differs from conventional CBT in that psychological flexibility is created through accepting rather than challenging psychological and physical experiences.[1,37,38]
- Mindfulness-based stress reduction (MBSR), which stresses body awareness and training in mindfulness meditation (i.e., nonjudgmental awareness of present-moment sensations, emotions, and thoughts), typically delivered in group format; research suggests effectiveness for coping with a variety of pain conditions (including rheumatoid arthritis, low-back pain, and MS) as well as improvements in pain intensity, sleep quality, fatigue, and overall physical functioning and well-being.[1,36,39-43]
- Emotional awareness and expression therapy, which is an emotion-focused therapy for patients with a history of trauma or psychosocial adversity who suffer from centralized pain conditions; patients are taught the effect of unresolved emotional experiences on neural pathways involved in pain and how to adaptively express those emotions.[1] Research indicates a positive impact on pain intensity, pain interference, and depressive symptoms.[44]
- Self-regulatory or psychophysiological approaches, which include biofeedback, relaxation training, and hypnotherapy, help patients develop control over their physiologic and psychological responses to pain.[1]
    - Biofeedback, which provides real-time feedback about physiologic functions such as heart rate, muscle tension, skin conductance, and has evidence of effectiveness for chronic headache in adults and children.[1,45]
    - Relaxation training and hypnotherapy, which alter attentional processes and heighten physical and psychological relaxation, and have empirical support in pain management.[1]

Complementary and Integrative Health Approaches

These therapies can be overseen by licensed practitioners and trained instructors and are used as standalone treatments or in combination with a multidisciplinary plan.[1] The following treatments may be considered for acute and chronic pain, according to patient status:[1]

- Acupuncture, which involves manipulating a system of meridians where "life energy" flows by inserting needles into identified acupuncture points; with its origins in Chinese medicine, acupuncture is received by an estimated 3 million Americans each year.[46] There is growing evidence of the therapeutic value of acupuncture in pain conditions that include osteoarthritis, migraine, and low-back, neck, and knee pain; however, existing clinical practice guidelines differ in their evidence analysis and recommendations for acupuncture use.[1] Risks are minimal when performed by a licensed, experienced, well-trained practitioner using sterile needles.[1]
- Massage and manipulative therapies, including osteopathic and chiropractic treatments, which may be clinically effective for short-term relief and are recommended in consultation with primary care and pain management teams.[1] Despite the paucity of rigorous studies, the lack of detail on massage types, and the smallness of sample sizes, positive effects of massage are recognized for various pain conditions that include postoperative pain, headaches, and neck, back, and joint pain.[1,47-50]
- MBSR, which is also discussed under behavioral health approaches, and which has evidence of statistically-significant beneficial effects for low-back pain, and is shown in a meta-analysis to significantly reduce the intensity and frequency of primary headache pain.[36,51]
- Yoga, which uses stretching, breathing, and meditation and has been shown to be therapeutic in the treatment of various chronic pain conditions, particularly low-back pain.[52-55] Risks are minimal, and yoga can generally be practiced safely, especially when delivered in group settings.[1,56]
- Tai chi, which originated as a Chinese martial art and uses slow movements and meditation, and which has demonstrated long-term benefit for osteoarthritis and other musculoskeletal pain conditions.[57,58] Like yoga, it is generally safe and has the benefits of a group setting and/or availability via telehealth.[1]
- Spirituality, which encompasses a broad range of resources and practices, such as prayer and meditation, has growing evidence of benefit for people with pain.[59]

  It has long been integral to palliative and supportive care, and is gaining support as a means to help patients cope with and manage ongoing pain.[1]

Non-Opioid Pharmacologic Options for Pain

Numerous non-opioid pharmacologic therapies are available for pain, and these should be tried or considered, alone or in combination, before initiating long-term opioid therapy.[1]

Acetaminophen (ACET) is used to treat mild-to-moderate pain without inflammation. All ACET products carry an FDA-required black box warning highlighting the potential for severe liver damage and potential for allergic reactions.[60] HCPs and patients should be aware of the dose levels from all prescribed and over-the-counter medication sources to avoid exceeding the recommended daily dosage.

Nonsteroidal anti-inflammatory drugs (NSAIDs) include aspirin, ibuprofen, naproxen, and cyclooxygenase-2 (Cox-2) inhibitors and are used to treat mild-to-moderate pain and inflammation. Indications are numerous and include arthritis, bone fractures or tumors, muscle pains, headache, and acute pain caused by injury or surgery.[1] Nonselective NSAIDs are those that inhibit the activity of both COX-1 and COX-2 enzymes and can be associated with gastritis, gastric ulcers, and gastrointestinal (GI) bleeding.[1] COX-2 inhibitors have fewer GI adverse effects.[1] Risks are elevated with NSAIDs for heart attack, stroke, GI bleeding or perforation, and renal and cardiovascular abnormalities, particularly at higher doses and longer duration of use.[61]

Anticonvulsants, such as gabapentin and pregabalin, have mild-to-moderate benefit for neuropathic pain syndromes, including postherpetic neuralgia and peripheral neuropathy and are also commonly used to treat migraine and as part of a multimodal approach to treating perioperative pain.[1] Adverse effects include drowsiness, cognitive slowing,[29] and a risk of misuse, particularly in people with a history of misusing opioids.[62] Gabapentin dose should be adjusted in chronic kidney disease.

Antidepressants, including selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants, are used in low doses for insomnia and neuropathic pain. Doses are typically lower for analgesia than those required to treat depression. SSRIs (e.g., fluoxetine, sertraline, citalopram, and paroxetine) have less analgesic effect compared with other antidepressant classes.[1] SNRIs (e.g., venlafaxine, duloxetine) are effective for a variety of chronic pain conditions, including musculoskeletal pain, fibromyalgia, and neuropathic pain, and are associated with less drowsiness, memory impairment, and cardiac conduction abnormalities than tricyclic antidepressants. Tricyclics (e.g., desipramine, nortriptyline, amitriptyline) are initiated at low doses and gradually titrated to effect. Depending on class, risks and adverse effects may include dry mouth, dizziness, sedation, memory impairment, orthostatic hypotension, urinary retention, cardiac conduction abnormalities, sexual dysfunction, weight gain, emotional blunting, and suicidal thoughts.[1,29] Second-generation tricyclic antidepressants (e.g., nortriptyline) tend to be better tolerated than first generation (e.g., amitriptyline). Withdrawal reactions are possible when antidepressants are suddenly stopped.

Musculoskeletal agents for pain and muscle spasm are for short-term use with sedation being a common adverse effect. Common medications used in pain treatment include baclofen, tizanidine, and cyclobenzaprine. Particular risks are notable with carisoprodol (toxicity, unclear therapeutic benefit) and benzodiazepines (SUD, respiratory depression leading to overdose) when prescribed in combination with opioids.[29] Considering the risks with carisoprodol and benzodiazepines and the availability of other agents, these medications are not recommended to treat pain from muscle spasm.[1]

Topical medications include lidocaine, ketamine, capsaicin, and anti-inflammatory drugs such as ketoprofen and diclofenac. Anti-inflammatory topicals are proven beneficial for musculoskeletal pain, as is capsaicin for neuropathic pain.[29]

Cannabis remains a Schedule I drug in the United States, defined by the Drug Enforcement Administration (DEA), as having no currently accepted medical use and a high potential for abuse.[1] Rigorous studies are lacking on the safety and efficacy of any specific cannabis product as a treatment for pain.[1] Expert views and systematic reviews[63,64] differ regarding the strength and quality of evidence for cannabis use, and the IASP does not endorse general use of cannabinoids for pain, citing lack of high-quality research. The evidence remains inconclusive to recommend the general use of cannabis for pain.

Little is known about the safety, efficacy, dose, and routes of administration of available cannabis products. Epidiolex (cannabidiol) [CBD] oral solution has been approved for the treatment of seizures associated with two rare and severe forms of epilepsy, Lennox-Gastaut syndrome and Dravet syndrome, in patients age 2 and older.[65] (It is THC that has the primary psychoactive component of marijuana, not CBD).

Importantly, the FDA has not approved cannabis for the treatment of chronic pain.[63] However, a number of patients with pain appear to be replacing opioids with cannabis. Marijuana is legal for medical use in several states, and public interest in cannabis and cannabis-derived products for pain treatment is rising.[63] Adverse events reported with cannabis use include psychotomimetic effects, anxiety and psychosis, cognitive dysmotivational syndrome, and learning deficits in adolescents.[66] Cannabis can also have hyperemesis effects, impair driving safety, and is linked to vascular events.[66] The topic of concurrent cannabis and opioid use will be covered later in this activity.

Opioids for Pain

Opioid analgesic effects are principally achieved by the opioid binding to and activating mu, kappa, and delta receptors in the endogenous opioid system. Drugs are classified according to their action at these receptors as full agonists, mixed agonist-antagonists, or antagonists (Table 2).

Table 2. Opioid Analgesic Classifications

Type	Generic Name	Notes/Cautions
Pure agonists	Codeine Dihydrocodeine Fentanyl Hydrocodone Hydromorphone Levorphanol Meperidine* Methadone Morphine Oxycodone Oxymorphone Propoxyphene	*Meperidine not recommended for long-term treatment or in patients with renal compromise due to toxicity risks
Agonist-antagonists	Partial agonist: Buprenorphine Mixed agonist-antagonists: Butorphanol Dezocine Nalbuphine Pentazocine	May produce withdrawal if started while patient receiving full opioid agonist
Pure antagonists	Naloxone Naltrexone	Administered to reverse opioid effects
Other	Tramadol Tapentadol	Dual action mu-agonist and serotonin–norepinephrine reuptake inhibitor Dual action mu-agonist and norepinephrine reuptake inhibitor

Full mu-agonists bind selectively to the mu-opioid receptor. When an antagonist occupies the receptor, it displaces the agonist and causes opioid withdrawal. Partial agonists, such as buprenorphine, have high receptor occupancy, some antagonistic effects, and low intrinsic activity at the site. Kappa opioid receptor agonists (including levorphanol, pentazocine, and butorphanol) have been used clinically but are associated with such side effects as dysphoria and hallucinations.

Buprenorphine has a reduced potential for respiratory depression and is considered safer than full agonists such as morphine, hydrocodone, and oxycodone.[1] Buprenorphine also acts as an antagonist at the kappa receptor, which is shown to reduce anxiety, depression, and the unpleasantness of opioid withdrawal.[1] Tapentadol and tramadol have dual modes of action as agonists at the mu receptor and SNRIs.[1] Considerations with dual-mechanism opioids include lowering of seizure threshold in susceptible patients and the risk of serotonin syndrome due to concomitant serotonin activity.[20]

Opioid delivery systems include oral, buccal, sublingual, spray, intravenous, intramuscular, intrathecal, suppository, and transdermal routes.[1] Administration includes ER/LA and IR/SA formulations. IR/SA opioids typically have a rapid onset from 10 to 60 minutes and a duration of action of 2 to 4 hours. In contrast, ER/LA opioids have a relatively slow onset of action of 30 to 90 minutes and longer duration of action from 4 to 72 hours. ER/LA opioids are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate for patients with existing opioid tolerance. The class of ER/LA opioids are not for use "as needed," not for mild pain, and not for acute pain or pain that not expected to persist for an extended duration:[67,68]

Opioid risks, warnings, and side effects include an FDA boxed warning about the serious risks for misuse, abuse, addiction, overdose and death that apply to all IR/SA and ER/LA prescription opioids.[69] These risks are present whenever opioids are misused but apply even at prescribed doses. The labels for opioid combination products containing ACET also warn of the potential for severe liver damage.[60] An FDA boxed warning details the risks of prescribing opioids and benzodiazepines together, a combination of medications that has increased in recent years but which is associated with extreme sleepiness, respiratory depression, coma, and death.[70] In addition, patients may suffer serious harm, including serious withdrawal symptoms, uncontrolled pain, and suicide, if opioids are suddenly discontinued or tapered too rapidly.[71,72] Concomitant drugs that act as inhibitors or inducers of various cytochrome P450 enzymes can result in higher or lower than expected blood levels of some opioids. Dosages should be reduced in the presence of hepatic or renal impairment.[68]

Certain cautions apply to specific opioid types, formulations, and delivery systems. Some opioids (e.g., methadone, buprenorphine) can prolong the QTc interval. Relative potency to oral morphine is intended as a general guide with additional conversion instructions included in each product's PI.[68] ER/LA opioid tablets should be swallowed whole, never crushed, chewed, broken, cut, or dissolved. Altering them in such ways may result in rapid release and absorption of a potentially fatal dose.[67,68] When necessary, some products may be sprinkled as pellets on applesauce and swallowed without chewing. Transdermal systems and buccal films should not be cut, torn, or damaged before use. Transdermal dosage forms should not be chewed or swallowed, and exposing patches to heat may lead to fatal overdose. Possible opioid side effects include but are not limited to:[1,61]

- Lightheadedness
- Dizziness
- Sedation
- Nausea and vomiting
- Drowsiness
- Mental clouding
- Constipation
- Hormonal deficiencies
- Pruritis
- Myoclonus
- Irritability
- Respiratory depression

Opioid pharmacokinetics influence the bioavailability of the drug, the production and elimination of metabolites, and the activity of metabolic enzymes.[73] Most opioids are metabolized through the liver microsomal cytochrome P-450 (CYP) system with CYP2D6 or CYP3A4 being responsible for much metabolism of opioids and many other drugs. Certain clinical applications are relevant. Slow metabolizers of CYP2D6 may gain little benefit from codeine, for example. Opioids metabolized through the CYP450 system, including codeine, oxycodone, hydrocodone, fentanyl, tramadol, and methadone, may have heightened or reduced CYP450-associated effects with drug combinations, while morphine, oxymorphone, and hydromorphone are not as prone to such interactions.[74] Codeine and tramadol should be avoided in breastfeeding women due to risks to the infant from ultra-rapid CYP2D6 metabolism in some people.[61,75] All opioids have similar pharmacodynamics, which describe effects in the body such as binding action and location to receptors, although individual patient responses may vary.[73]

Drug-Drug interactions are possible with opioids.[68] Co-ingesting CNS-depressants that include alcohol, benzodiazepines, sedatives, hypnotics, tranquilizers, and tricyclic antidepressants can potentiate the sedation and respiratory depression caused by opioids. Alcohol can cause rapid release of ER/LA opioid formulations leading to an increased drug level. Combining opioids with monoamine oxidase inhibitors (MAOIs) can increase respiratory depression and cause serotonin syndrome with certain opioids. Opioids induce the release of antidiuretic hormone, reducing the efficacy of diuretics. Initiating CYP 3A4 inhibitors or discontinuing CYP 3A4 inducers can result in higher than expected opioid blood levels leading to overdose.

Opioid contraindications. There are some absolute contraindications for initiating a trial of long-term opioid therapy that include:[20]

- Known hypersensitivity to active ingredients or other components of opioid analgesics.
- Significant respiratory depression or compromise.
- Acute or severe bronchial asthma.
- Known or suspected paralytic ileus and gastrointestinal obstruction.
- Evidence for or history of diversion of controlled substances (e.g., forged prescriptions, pharmacy robberies, selling own prescription drugs, theft of others' drugs).

Although the combination is sometimes used, the Department of Veterans Affairs/Department of Defense (VA/DoD) practice guideline lists concomitant use of benzodiazepines as a contraindication to initiating a trial of long-term opioid therapy.[20] The Centers for Disease Control and Prevention (CDC) recommends avoiding prescribing opioids and benzodiazepines concurrently whenever possible but allows for rare instances when the combination may be indicated (e.g., severe acute pain in the presence of long-term, stable, low-dose benzodiazepine therapy).[61]

Medication errors may result from miscommunication, packaging design, confusion caused by similar drug names, and other sources. Patient counseling and education can help guard against medication errors.

Methadone for pain presents special clinical challenges due to a long and variable half-life, risk for toxicity due to accumulation in plasma concentrations during the several days necessary to achieve steady-state, and risk for cardiac toxicities due to prolongation of the QTc interval.[76-78] Methadone-related deaths have occurred in disproportionate numbers relative to the frequency with which it is prescribed for pain.[61] Methadone is only for patients whose severe pain is unrelieved by other opioids. Close monitoring is critical when initiating methadone and during dose changes, and caution is needed in patients with heart disease or taking medications with concurrent QTc interval effects. Patients should be assessed for cardiac health ahead of being prescribed methadone, and an initial ECG may be advisable, particularly if the patient has cardiac disease or risk factors. If methadone is initiated, it should be started at a very low dose (e.g., 2.5mg tid) and slowly titrated (e.g., by no more than 25%-50%, no more frequently than weekly.[76,77] In adults on relatively low previous opioid doses (e.g., <40–60 mg per day of morphine or equivalent), experts suggest a starting dose of 2.5 mg tid with initial dose increases of no more than 5 mg daily every 5 to 7 days.[79]

When switching to methadone from higher previous doses of another opioid, consider starting methadone at a dose that is 75% to 90% less than the calculated equianalgesic dose (no higher than 30 to 40 mg per day) with initial dose increases of no more than 10 mg per day every 5 to 7 days.[79] It is important to withhold methadone if there is evidence of sedation.[79] Bear in mind that pain relief from a methadone dose lasts only 4 to 8 hours, but methadone remains in the body much longer (8 to 59 hours).[78] Patients should be counseled never to exceed the prescribed dose, not to mix with alcohol or other unauthorized substances, and to take methadone doses only as scheduled, not as needed. HCPs without experience and knowledge of methadone should seek expert consultation before prescribing it.[76]

Abuse-Deterrent Opioids

The FDA defines abuse-deterrent properties as those that deter but do not prevent all abuse (i.e., misuse).[80] Common technologies incorporate physical barriers to deter crushing and chewing, chemical barriers to resist extraction in common solvents of the active ingredient for injection, or opioid antagonists to block euphoria when a pill is altered. These formulations have been suggested as a way to reduce harm from prescribed opioids. The FDA cautions that abuse may still occur by swallowing intact pills.

Data on abuse-deterrent properties are included in the Drug Abuse and Dependence section of the drug's prescribing information under 9.2 Abuse. If missing or located elsewhere, the FDA does not consider the product abuse deterrent. The label also contains information on the types of studies conducted and the routes of abuse the formulation is expected to deter (e.g., oral, intranasal, insufflation, intravenous). Thus far, 10 opioid formulations have received abuse-deterrent labeling from the FDA. Post-marketing studies for the approved formulations are in their infancy, and new deterrent formulations are continually in development.[81]

Considerations with Opioids in Special Populations:[20]

Women/Pregnant Women

Several diseases with a high burden of pain are more common in women or are sex specific. These include endometriosis, musculoskeletal and orofacial pain, fibromyalgia, migraines, and abdominal and pelvic pain.[1] Sex differences extend to the pain response itself, and recent scientific literature suggests that, compared with men, women experience more pain, are more sensitive to painful stimuli, report more intense pain, and are more likely to misuse prescription opioids, though there remain many research gaps related to women's health and pain.[1]

During pregnancy, HCPs and patients together should carefully weigh risks and benefits when making decisions about whether to initiate opioid therapy.[61]

All women should be informed of the risks of long-term opioid therapy to the developing fetus during current or potential future pregnancies, including a drug withdrawal syndrome in newborns called neonatal opioid withdrawal syndrome (NOWS).[61] An estimated 32,000 babies were born with NOWS in 2014, an five-fold increase from 2004.[82] Babies born to women who are taking opioids are at risk for birth defects (including neural tube defects, congenital heart defects, and gastroschisis), preterm delivery, poor fetal growth, and stillbirth.[61] Given the risks during pregnancy and postpartum, HCPs are encouraged to include obstetricians and gynecologists as part of the pain care management team.[1]

When caring for pregnant women who are prescribed opioids, HCPs should arrange for delivery at a facility prepared to evaluate and treat NOWS.[61] Women with SUD should be offered evidence-based treatment. In pregnant women with OUD, the risk of opioid exposure from opioids used to treat OUD should be discussed and balanced against the risk of untreated OUD, which might lead to illicit opioid use associated with outcomes such as low birth weight, preterm birth, or fetal death.[83]

Pain management guidelines in Tennessee recommend the following measures when treating women of child-bearing age:[84]

- Every woman with reproductive capacity should discuss with the HCP a method to prevent unintended pregnancy when initiated on opioids.
- Agreement should be obtained to inform the HCP if the woman becomes or intends to become pregnant while prescribed opioids.
- Women who plan to become pregnant should be counseled on the risks of opioid exposure to the fetus and referred to an obstetrician.
- The obstetrician and HCP should work together to encourage compliance with chronic pain management and prenatal care.
- All newly pregnant women should have a urine drug test administered by the appropriate women's health practitioner.
- If a urine result is positive for unprescribed controlled substances or illicit drugs during a prenatal visit, the woman should have another upon admission for delivery to help identify the infant at risk for NOWS.

Older adults

People who are ≥65 years require cautious opioid dosing and management as they may have numerous co-occurring medical problems with treatments that increase the risk for polypharmacy and harmful drug interactions.[77] Their risk for falls and cognitive effects with sedating medications and their sensitivity to analgesic effects are increased. In addition, prescription drug or other substance use may be difficult to spot, mimicking symptoms of common conditions such as dementia, diabetes, and depression. Initial doses should be 25–50% lower than in those who are younger.[85] The VA/DoD practice guideline suggests that tramadol has benefits in older patients because of its partial mu agonist activity and demonstrated safety profile when combined with ACET, though drug-drug interactions should be evaluated when prescribing tramadol.[20]

Children and adolescents

Evaluating the origin of the pain condition is important in the pediatric age group. If pain is not controlled, children are at risk for persistent pain as they grow to adulthood.[1] Use of multidisciplinary treatments is advised as is treatment of psychological conditions to manage difficulty coping, anxiety, and depression. It has been suggested that opioid analgesia may be indicated for certain chronic pediatric conditions; however, current guidelines generally exclude this population from treatment recommendations, and scientific investigation is scant into the indications and safety concerns with opioids for the pediatric population.[86] Accidental exposure to and ingestion of opioids can result in death.

People with renal and hepatic impairment

Extra caution and increased monitoring is necessary when initiating and titrating opioid doses in people with renal and hepatic impairment.[61] In patients with renal compromise, accumulation resulting in toxicity has been observed in case studies; therefore, it is advised to monitor for opioid toxicity and to use non-opioids when possible.[87]

People with sickle cell disease

Sickle cell disease, which affects an estimated 90,000 people in the United States, is characterized by complex acute and chronic pain symptoms.[88] The disease is particularly prevalent among African Americans. According to the HHS Inter-Agency Task Force on best pain management practices, unpredictable, episodic exacerbations of acute pain pose a challenge to patients with sickle cell disease, and this pain generally has not responded to non-opioids prior to presentation.[1] Limited access to oral opioids at home for the treatment of unplanned acute pain can result in increased use of health care services that could have been avoided. Stigma, negative practitioner attitudes, and perceived racial bias may further complicate care. Effective models of pain treatment for patients with sickle cell disease include multidisciplinary teams of practitioners with experience treating the disease.

Racial and ethnic disparities in pain care

Evidence documents disparities in health care in racial and ethnic minority populations, often related to such factors as lack of insurance or primary care access, discrimination, environmental barriers to self-management, lower likelihood of being screened for or receiving pain treatment and more.[1,20] The disparities extend to mental health care and addiction treatment where access to care is very limited for Black individuals, Indigenous individuals, and other individuals of color. There is evidence that racial and ethnic minority populations prefer seeking treatment in primary care over specialty mental health settings.[89]

Active duty military, reserve service members, and veterans

Pain management in veterans and active military members can be complex. Combat-related injuries include ballistic wounds, burns, over-pressurization, and blunt trauma.[1] In addition, complications can arise from PTSD and traumatic brain injury.[1] Delaying pain treatment can lead to acute pain becoming chronic.[90] Veterans are also at risk for death by suicide, a risk compounded when pain conditions are present. HCPS can discuss suicide risk with service members and veterans and address pain treatment as part of suicide prevention as a recognized public health approach.[1]

Medical complexities of pain care

Genetic and phenotypic variations influence how quickly or well different people metabolize opioids and other drugs.[73] Medical conditions, including kidney and liver disease, also cause variations in opioid metabolism.[73] The FDA has approved some tests, for example, one aimed at determining whether a patient is a CYP2D6 ultra-rapid metabolizer.[75] However, little data actually exist to inform the practice of pain management, and these tests are not routinely performed.[91] HPCs should be aware that genetics is one of many factors that may affect drug metabolism and responses, so patient experience with certain pain treatments or medications should be used to develop individualized treatment plans.

Definitions Related to Opioid Use and Misuse

The HHS Inter-Agency Task Force on best pain management practices endorsed a set of definitions to guide conversations and understanding of frequent terms related to opioid use and misuse.[1] These definitions are shown in Table 3.

Diversion

Most people who misuse prescription opioids are given them freely by friends or family members, though some people buy or steal them.[93] About a third of people who misuse opioids get them by prescription from one doctor.[93] Many misused opioids became available in the community because they were left over from prescriptions for acute pain.[94] It is incumbent on the HCP to remember that, although most people who are prescribed opioids for pain do not misuse them, it is possible that some people who visit a medical facility for pain are instead seeking opioids to divert for misuse or illegal sale.

Creating Pain Treatment Plans

All pain management begins with identifying the cause or causes of pain and the biopsychosocial mechanisms that contribute to its severity and associated disability.[1] An effective treatment plan is built out of a full evaluation to establish diagnosis and emphasizes individualized patient-centered care. When persistent pain pertains to a specific disease condition or patient population, HCPs are advised to seek out evidence-based practice guidelines that are relevant.[1] The patient's pain type and previous treatments should be evaluated to see if opioid therapy is likely to be effective. The HCP should consider whether medical comorbidities, such as sleep apnea, may increase risk of respiratory depression, whether other available therapies have better or equal evidence, and whether thorough patient evaluation indicates the patient is likely to adhere to the treatment plan.

Treatment plans should be revisited and adjusted frequently to ensure goals are being met and any adverse effects of therapy are addressed. The success of a pain management plan is highly dependent on the therapeutic alliance established between the patient and the HCP.

Managing Acute Pain

For acute pain, non-opioids may offer effective management and should be utilized preferentially, alone or in combination with opioids (when indicated) to increase pain control and spare opioid doses.[22] Much acute pain is manageable with rest, over-the-counter medications, or a short course of opioids and resolution of the underlying cause (e.g., trauma, surgery, illness). Objective signs of an acute, painful medical condition (e.g., bone fracture or imaging that reveals kidney stones) are examples for when opioids are likely indicated. Prompt management of acute pain is necessary to prevent progression to a chronic state.[22]

When opioids are indicated, the therapeutic goal is to prescribe the lowest dose that controls pain for a duration lasting only as long as the acute phase. Leftover pills from acute pain prescriptions may later become a chief source of diverted and misused opioids. A systematic review found that 42% to 71% of opioids obtained by surgical patients went unused.[94] Prescriptions beyond three days are usually unnecessary,[61] while more severe episodes rarely need more than 7-14 days, although there are exceptions.[61,85] Be aware that localities and states may have strict regulations governing maximum duration of prescriptions for acute pain. In nearly all cases, HCPS should not prescribe ER/LA opioids for acute pain. It is worth considering that long-term opioids typically are not recommended for nonspecific back pain, headaches, or fibromyalgia, if the HCP should see a patient experiencing acute pain flares occurring with these conditions.[20]

Table 3. Definitions Related to Opioid Use and Misuse[1]

Term	Definition
Physical dependence	• Not the same as addiction • Occurs because of physiological adaptations to chronic exposure to opioids • Withdrawal symptoms occur when medicine or opioid is suddenly reduced or stopped or when antagonist is administered • Symptoms can be mild or severe and can usually be managed medically or avoided through slow opioid taper
Tolerance	• Same dose of opioid given repeatedly produces reduced biological response • Higher dose of opioid is necessary to achieve initial level of response
Misuse	• Taking medication in a manner or dose other than as prescribed • Taking someone else's prescription, even if for a medical complaint like pain • Taking medication to feel euphoria (i.e., to get high) • Nonmedical use of prescription drugs refers to misuse
Addiction	• Primary, chronic medical disease of brain reward, motivation, memory, and related circuitry • Dysfunction in circuits leads to characteristic biological, psychological, social, and spiritual manifestations as individual pathologically pursues reward and/or relief by substance use and other behaviors • Characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and dysfunctional emotional response • Involves cycles of relapse and remission • Without treatment or recovery activities, is progressive and results in disability or premature death
Opioid-use disorder	• A problematic pattern of opioid use leading to clinically significant impairment or distress • Defined by 11 criteria in the DSM-5* over a 12-month period • Previously classified as "opioid abuse" or "opioid dependence" in DSM-4 • Severe opioid-use disorder also referred to as "opioid addiction"

*DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition;[92] diagnostic criteria given later in this activity

Be aware also that patients who seek opioids to misuse may utilize emergency departments or urgent care for this purpose. The American College of Emergency Physicians (ACEP) has identified acute low back pain and exacerbations of chronic pain as common presenting complaints in the emergency department and recommends assessing whether non-opioid therapies would be adequate pain treatment, reserving opioids for severe pain that would be unresponsive to other therapies.[95] If opioids are indicated, the ACEP recommends prescribing the lowest practical dose for the shortest duration, considering the patient's risk for opioid misuse or diversion.[95] Checking the state prescription database ahead of prescribing opioids for acute pain can help ensure the patient is receiving the appropriate quantity of opioids for the pain.[1] If pain from surgery or trauma persists beyond the expected healing period, HCPs should reevaluate the diagnosis and treatment plan.

Assessing the Risk of Transition from Acute to Chronic Pain

Most cases of chronic pain begin as acute pain, and evidence suggests that prolonged exposure to pain leads to CNS changes that can transform the experience to a chronic syndrome.[22] Studies suggest that one-third of patients have progressively worsening pain intensity postoperatively,[22] and most research on risk factors for transitioning from acute to chronic pain takes place in surgical settings. Established risk factors include younger age, female gender, catastrophizing, low socioeconomic status, preoperative pain, impaired diffuse noxious inhibitory control, type and duration of surgery, injury to specific nerves, severity of acute pain, and, possibly, prior exposure to radiation therapy and chemotherapy.[22] The high association of pain severity with subsequent chronic pain development boosts the rationale for comprehensive pain assessment and treatment in the perioperative setting.[22]

It is clear that psychological factors contribute to the pain experience overall and pose risk for chronicity. Depression after injury is an important predictor associated with reduced odds for recovery.[96] In people recovering from musculoskeletal trauma, catastrophic thinking (a psychological factor that responds to CBT) predicted pain intensity and disability at five-to-eight months post-injury.[34] Psychological interventions, following proper evaluation and diagnosis, can play a central role in reducing disability. When delivered before surgery, psychological interventions are shown to reduce postsurgical pain and opioid use[97,98] and may help prevent progression from acute to chronic pain.

A systematic literature review found support for two screening tools that may be useful in helping HCPs predict the likelihood of a transition from acute or subacute to chronic low back pain.[99] These tools are the STarT Back Screening Tool and the Örebro Musculoskeletal Pain Questionnaire, which stratify patients in into low-, medium-, and high-risk categories and were found to be valid, reliable and to have predictive value. Intense widespread pain (especially when it is increasing) and fear avoidance were found to predict the transition to chronic pain. Incorporating one of these tools or evaluating common predictors in acute pain can help HCPs identify patients at risk in order to treat them early or refer them for specialist management to prevent the trajectory to chronic pain.

Managing Cancer-Related Pain

More than 14 million cancer survivors live in the United States.[1] An estimated 40% of cancer survivors experience persistent pain as a result of treatments such as surgery, chemotherapy, and radiation therapy.[1] All HCPs who treat patients with active cancer or with cancer-related pain should assess for, recognize, and treat pain at every encounter. Remember that the CDC guideline for opioid prescribing affirms the use of opioids when benefits outweigh risks and warns against opioid tapering or discontinuation when opioid use may be warranted, such as in treatment of cancer pain or at the end of life.[72]

With cancer-related pain, HCPs are encouraged to look beyond narrow treatment choices and incorporate multimodal treatments in a multidisciplinary treatment plan.[1] Cancer survivors should be evaluated for a recurrence or secondary malignancy with any new or worsening pain symptoms.[85]

Managing Pain in Palliative Care and at End of Life

Persistent, significant pain is common in patients with a limited prognosis, such as those in hospice and palliative care environments. The goal in palliative care is to keep the patient comfortable. HCPs should assess and address pain at every encounter, using multimodal and multidisciplinary care as part of the care management plan as indicated.[1]

In end-of-life care, pain control may be balanced against meaningful priorities the patient may have such as mental alertness and maximal interactions with loved ones. Pain assessment may be challenging in the context of reduced consciousness. Signs of discomfort include more rapid breathing or heart rate. Rectal and transdermal routes can be especially valuable at the end of life when the oral route is precluded because of reduced or absent consciousness, difficulty swallowing, or to avoid nausea and vomiting.[100]

Managing Chronic Noncancer Pain

To apply best practices in chronic noncancer pain treatment, HCPs should recognize and treat pain promptly, involve patients in the pain care plan, reassess and adjust the pain care plan as needed, monitor patient progress toward treatment goals, monitor patient adherence to any treatment agreements, and document all pain management outcomes in the patient medical record.

The goals of treatment should be meaningful to the patient and contain measurable outcomes of improvement that include pain relief, functionality, quality of life, and activities of daily living.[20,61,85] Even patients with pain conditions or injuries that make complete cessation of pain unlikely can set goals such as sleeping through most nights, returning to work, walking a set distance, or participating more fully in family activities. The self-efficacy involved in collaborating on these goals can help patients gain greater control over their pain and their lives.

Choices in medications are based on pain diagnosis and severity; comorbidities as established through medical history, physical exam, relevant diagnostic procedures; patient response; and a risk-benefit assessment to increase the likelihood that benefits outweigh risks. It is important to differentiate between nociceptive and neuropathic pain and to thoroughly evaluate the patient to aid in an accurate diagnosis, identifying the generator of pain whenever possible. Neuropathic pain can be difficult to manage and generally requires a combination of pharmacologic and nonpharmacologic approaches.[23] Choices of medications for neuropathic pain that provide the most relief include anticonvulsants, antidepressants, or local anesthetics. NSAIDs are not considered effective treatments for neuropathic pain, and opioids should be reserved for patients who did not respond to other therapeutic options.[23,61]

For osteoarthritis, ACET and NSAIDs are considered first-line and second-line medications, respectively, and many guidelines recommend NSAIDs and ACET as first-line therapies for low-back pain.[61] Corticosteroid injections are generally recommended for hip and knee osteoarthritis.[101] Expert guidelines usually now recommend against ongoing opioid therapy for nonspecific back pain, headaches, and fibromyalgia.[20]

Whenever possible, nonpharmacologic therapies and self-management strategies should be optimized.[27] Noninvasive interventions in specific conditions that have sustained small improvements in pain and function for one month or longer post treatment without serious harms are shown in Table 4.[30] A trial of opioids, when indicated, should be part of a comprehensive treatment approach, typically in combination with one or more treatment modalities.[20]

Assessing Pain

A patient's initial visit for evaluation of a pain problem should include a physical exam and a patient interview to gather and document medical history and pain assessment. One should obtain a complete history of current and past substance use and misuse to include prescription drugs, illegal substances, alcohol, and tobacco. Social history is also relevant and includes employment, marital history, and family status.[77] Women should be screened for contraceptive use and pregnancy or breastfeeding status or intent.[61] Previous treatment records, including any pertinent clinical notes of treatments tried, and laboratory and imaging results should be reviewed whenever possible and retained in the current patient record.

Table 4. Noninvasive, Nonpharmacologic Treatments for Specific Pain Conditions[30]	
Pain Condition	**Treatment**
Chronic low back pain	Exercise, psychological therapies (primarily cognitive behavioral therapy), spinal manipulation, low-level laser therapy, massage, mindfulness-based stress reduction, yoga, acupuncture, multidisciplinary rehabilitation, tai chi
Chronic neck pain	Exercise, low-level laser, Alexander Technique, acupuncture
Knee osteoarthritis	Exercise, ultrasound
Hip osteoarthritis	Exercise, manual therapies
Fibromyalgia	Exercise, cognitive behavioral therapy, myofascial release massage, tai chi, qigong, acupuncture, multidisciplinary rehabilitation
Chronic tension headache	Spinal manipulation

Pain should be assessed by its severity (to include pain intensity, pain-related distress, and interference with daily activities), its temporal characteristics (to include onset, duration, whether it is continuous, has recurrent episodes with painless intervals, or is continuous with times of pain exacerbation). Psychological and social factors can contribute to the pain experience, which is why these issues should be included in the patient interview and documented in the record. Recording these factors will assist with documenting what special pain management needs a patient has as well as what level of disability.[23] Good questions to ask the patient include what relieves or increases the pain, how it affects their daily lives and functioning, and what goals they have for pain relief and improved function.

A number of evidence-based, pain assessment tools are available for clinical practice:

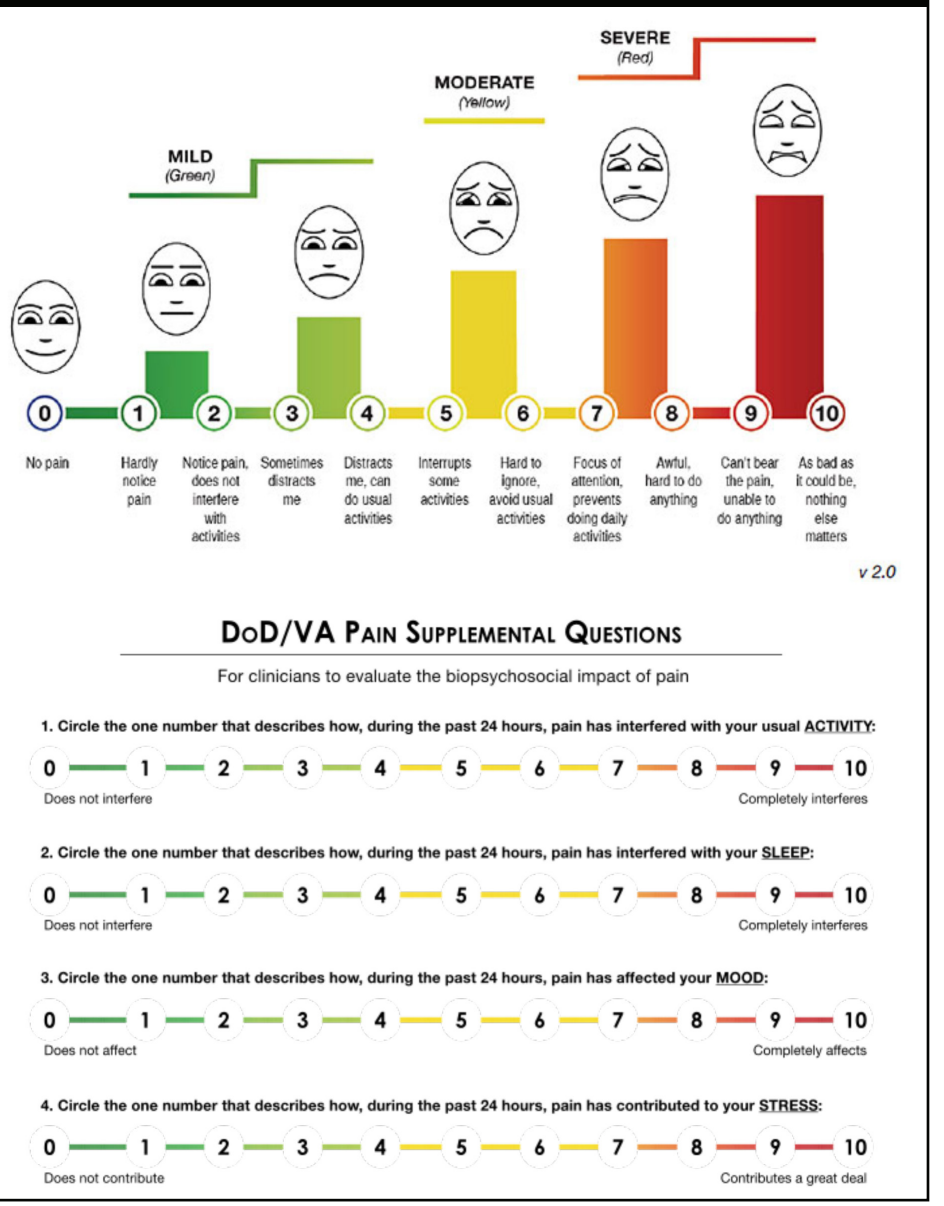
- The Visual Analogue Scale (VAS) and Numerical Rating Scale (NRS) are quick tools to measure pain severity that are sensitive, validated, and widely-used.[102]
- The Brief Pain Inventory (BPI) has good sensitivity, reliability, and validity for pain severity and interference-with-function items, including assessments of mood and sleep.[103,104]
- The Pain, Enjoyment of Life, and General Activity Scale (PEG) was created to assist management of chronic pain in primary care settings.[105] It is based on the BPI and has rating scales to measure past-week pain, pain interference, functional components, and quality of life.
- The McGill Pain Questionnaire (MPQ) assesses pain descriptors (sensory, evaluative, and affective).[102] With good validity and reliability, the MPQ is useful for helping patients describe their subjective pain experience but requires a good vocabulary when self-administered. The MPG is also available as a short form.
- The Multidimensional Pain Inventory has been validated for multiple chronic pain conditions for categorizing how well patients cope with chronic pain as adaptive, dysfunctional, or interpersonally distressed.[106,107]

Numeric pain scales, such as the VAS or NRS, have limitations in that they provide only a snapshot of the pain on a given day and do not necessarily reflect the impact of pain on the patient's life. One should also consider other clinical signs and symptoms and to make treatment decisions to further therapeutic goals meaningful to the patient rather than basing treatments solely on a pain scale number.

HCPs should also screen and monitor patients for factors associated with poor outcomes and substance abuse, such as sleep disturbance, mood disorder, and stress. HCPs are encouraged to consider use of a scale such as the Defense and Veterans Pain Rating Scale (DVPRS) (Figure 3).[1,108]

The DVPRS is a graphic tool with a numeric rating scale in which each pain level has descriptive word anchors, facial depictions of pain, and color coding that coincides with pain severity categories. The DVPRS also includes supplemental questions for general activity, sleep, mood, and level of stress. This or other numeric pain scales may be particularly useful for assessing pain in patients who have language deficits or other issues with communicating their experience of pain.

Figure 3. The Defense and Veterans Pain Rating Scale and Supplemental Questions[108]



The PEG scale can be very useful in primary care or busy practices to assess pain, functioning, and quality of life.

Assessing Mental Health

Screening tools to assess patients with pain for mental health disorders ahead of prescribing opioids include:

- Patient Health Questionnaire-2 (PHQ-2), a two-item screen for depressive disorder that leads to more detailed assessment if either item is positive.[109] The PHQ-2 is available at the following link: https://www.hiv.uw.edu/page/mental-health-screening/phq-2
- Patient Health Questionnaire-9 (PHQ-9), this nine-item screen for depressive disorder may be used initially or as a follow-up to the PHQ-2.[110] This tool and its variations are brief, reliable, valid, and easy to score. The PHQ-9 is available at the following link: https://www.hiv.uw.edu/page/mental-health-screening/phq-9
- The reliable and valid Beck Depression Inventory-II (BDI-II) is a self-report measure of depression severity.[111] This 21-item tool is available here: http://www.hpc-educ.org/Files/Danz/BDII.pdf
- Suicidal ideation is addressed by items on the PHQ-9 and BDI-II. This is an important assessment for patients with chronic pain.
- The Beck Anxiety Inventory (BAI) emphasizes somatic components of anxiety[112] and can be found here: https://www.gphealth.org/media/1087/anxiety.pdf
- The Generalized Anxiety Disorder-7 (GAD) and GAD-2 are validated and recommended to assess for generalized, panic, and social anxiety disorders, and PTSD.[61,113,114] These tools are available here: PMID: 32582485

Newer systems such as the Stanford-developed and implemented Collaborative Health Outcomes Information Registry offer more in-depth pain assessment through the use of item banks that capture many physical, psychological, and social functioning domains.[115]

Assessing Social History, Including Substance Use

Patients to be treated with opioid therapy should be screened for the risk of opioid misuse and OUD and monitored regularly. Misuse of prescription opioids is common whether from casual sharing of prescription pills, recreational or experimental use by non-patients (including adolescents), all the way up to and including development of OUD in at-risk populations. Yet clinically it is not always easy to differentiate between appropriate use of prescribed opioids and behavior that may indicate a problem. There is reason to suspect that a pattern of seeking opioids from multiple sources is a strong indicator of misuse and possible OUD.[116]

A list of behaviors suggestive of opioid misuse is shown in Table 5.[116,117]

A number of risk factors are associated with poorer outcomes in opioid therapy.[101] These factors include:[118]

- Nonfunctional status (e.g., severe physical debility) due to pain
- Exaggeration of pain
- Unclear etiology for pain
- History of rapid opioid dose escalation
- Young age (<30 years)
- Tobacco use
- Poor social support
- Personal history of SUD
- Family history of SUD
- Psychological stress
- Psychological trauma
- Psychological disease
- Psychotropic substance use
- Focus on opioids
- Sexual trauma
- History of legal problems
- History of SUD treatment
- Craving for prescription drugs
- Mood swings/disorders
- Childhood adversity, adverse childhood experiences
- Social environments that encourage illicit substance use

The HHS Inter-Agency Task Force on best practices in pain management emphasizes sleep disturbances, mood disorders, and stress as factors that put patients at risk for poorer outcomes and substance use.[1] HCPs may identify risk factors from patient and family history and current biopsychosocial evaluation.

Assessing for Risk of Overdose

Respiratory depression leading to fatal or nonfatal overdose is a chief risk with opioids. Risk factors for overdose in people taking opioids medically or nonmedically include:[119-123]

- Middle age
- History of SUD
- Comorbid mental and medical disorders
- High opioid dose (>90 mg morphine equivalents, although risk is present at any dose)
- Recent upward titration of opioids (within the first 2 weeks)
- Recent opioid rotation
- Methadone use

Table 5. Patient Behaviors Suggestive of Opioid Misuse, Diversion, Abuse, and Addiction (list not exhaustive)

Behavior Category	Behavior
Observed clinically:[116]	Over-sedated/intoxicated Opioid overdose
Laboratory findings:[116]	Abnormal (i.e., inconsistent) urine or blood screen
Unusual healthcare utilization:[116]	Reports multiple pain causes Resists therapeutic changes/alternatives Cancels/no shows pain clinic visits Has persistent/non-modifiable pain Requests refills instead of clinic visit Gets prescriptions from multiple practitioners without their coordination or knowledge
Risk factors for getting prescriptions from multiple practitioners without their coordination or knowledge:[116]	Age ≤65 Concurrent use of benzodiazepines Mood disorders Back pain Abuse of non-opioid drugs
Patient reported (primary care population):[117]	Requested early refills Increased dose on own Felt intoxicated from pain medication Purposely over-sedated oneself Used opioids for purpose other than pain relief Lost or had medication stolen Tried or succeeded in obtaining extra opioids from other doctors Used alcohol or other non-prescribed substances to relieve pain Hoarded pain medication

- Benzodiazepine use
- Antidepressant use
- Unemployment
- Use of non-prescribed illicit substances
- Recent release from jail or prison
- Recent release from substance treatment program
- Sleep apnea
- Heart or pulmonary complications (e.g., respiratory infections, asthma)
- Pain intensity

Higher dose adds risk for opioid-related overdose but other risk factors contribute, and no dose is completely safe.[124] Although the CDC guideline identified a dose limit of 90 morphine milligram equivalents (MMEs) daily after which caution is advised, another study involving 2.2 million North Carolinians did not show evidence of a distinct risk threshold and found much of the risk at higher doses to be associated with co-prescribed benzodiazepines.[122]

Evidence is strong that prescribing opioids together with benzodiazepines increases risk for overdose,[20] and evidence suggests that co-prescription of opioids and gabapentinoids also may increase overdose risk.[20]

Consider use of the Veterans Administration-developed Risk Index for Overdose or Serious Opioid-induced Respiratory Depression (RIOSORD) to assess for the risk of a serious opioid-related respiratory depression event in patients treated with medical opioids (available here: https://paindr.com/wp-content/uploads/2015/09/RIOSORD-tool.pdf). This tool showed nearly 90% predictive accuracy in a Veterans Administration case–control analysis of close to 9,000 veteran patients[125] and was subsequently validated in the commercial insurance records of a nonveteran population of approximately 18 million medical users of prescription opioids.[126]

Screening for Opioid Misuse Risk

Several screening tools are available to help HCPs detect current opioid misuse or risk that a patient may develop misuse or OUD during the course of opioid therapy. None has been associated with a high degree of predictive accuracy;[1,61] however, they are generally recommended in expert guidelines for their clinical utility (Table 6). Most of the tools in Table 6 are specific to opioid-treated patients with pain. The HHS Inter-Agency Task Force has also cited the Drug Abuse Screening Test[127] and the Alcohol Use Disorders Identification Test[128] as validated tools.[1]

HCPs should select the tool that fits best into their clinical practice, treating assessment as routine and encouraging patients to share information honestly. Even single questions, such as, "How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?" can be effective means of screening for drug use if implemented consistently.[129] An answer to the single question of one or more is considered positive and was found in a primary care setting to be 100% sensitive and 73.5% specific for the detection of a drug-use disorder compared with a standardized diagnostic interview.[61,129] The information gained from screening is documented in the patient record and used to assist selection of the best treatments, including medication classes and delivery systems, to facilitate ongoing monitoring to help mitigate potential opioid misuse, and to inform whether SUD treatment and mental-health referrals are warranted.

A baseline urine drug test (UDT) should take place before opioids are prescribed or continued.[20,61,77] Usefulness of a UDT includes identifying the presence of prescribed medications as well as unauthorized prescription and illegal drugs, helping to guide clinical decisions, and serving as an alert to potential drug-drug interactions.

Immunoassay testing done at the point of care (POC) can help quickly establish whether a new patient has recently ingested illegal drugs or other opioid and prescription drugs but typically cannot isolate specific opioids.[137] If POC test results are inconsistent with medical direction, the next step is a quantitative evaluation, usually via gas chromatography/mass spectrometry (GC/MS) technology or liquid chromatography dual mass spectrometry (LC/MS/MS). These tests can detect actual drugs and their metabolites. Some laboratories offer definitive testing via LC-MS/MS that may be given as the initial test; however, most guidelines still suggest immunoassay ahead of confirmatory testing due to cost concerns.[137]

A query of the state prescription drug monitoring program (PDMP) should also take place before opioids are initiated or continued.[20,61,77] These importance checks of the patient's past and present opioid prescriptions are done at initial assessment and during the monitoring phase. PDMP data can help to identify patients who have had multiple practitioner episodes or potentially overlapping prescriptions that place them at risk of a misuse or drug interaction problem. The use of an PDMP is also aimed at stopping the spread of opioid misuse and diversion as a public health problem.

If baseline UDT and PDMP checks indicate unauthorized prescriptions or there are other signs suggestive of opioid misuse, the results should be discussed with the patient and, if OUD or another substance-use issue is suspected, treatment should be offered and/or a specialist referral can be given. More will follow on using UDT and PDMP checks for periodic monitoring during the course of opioid therapy.

BEFORE MOVING ONTO THE NEXT SECTION, PLEASE COMPLETE CASE STUDY 1 ON THE NEXT PAGE.

Table 6. Screening Tools for Risk of OUD in Opioid-Treated Patients

Tool	# of Items	Administered	Approximate Time to Complete
For Use Prior to Initiating Opioid Therapy			
Opioid Risk Tool (ORT)[130]	5	Health-care practitioner	1 min
Revised Screener and Opioid Assessment for Patients with Pain (SOAPP-R)[131]	24*	Patient	5 min
Diagnosis, Intractability, Risk, Efficacy (DIRE)[132]	7	Health-care practitioner	2 min
Pain Medication Questionnaire (PMQ)[133]	26	Patient	10 min
For Use During Opioid Therapy			
Current Opioid Misuse Measure (COMM)[134]	17	Patient	10 min
Patient Version Prescription Drug Use Questionnaire (PDUQp)[135]	31	Patient	20 min
Brief Initial Drug Screenings Not Specific to Pain Population			
CAGE-AID (Adapted to Include Drugs)[136]	4	Health-care practitioner	1 min
Drug Abuse Screening Test (DAST)[127]	10	Health-care practitioner or patient versions	5 min
Alcohol Use Disorders Identification Test[128]	10	Health-care practitioner or patient versions	5 min
*4- and 12-item SOAPP formats available			

Case Study 1

Instructions: Spend 5-10 minutes reviewing the case below and considering the questions that follow.

Jonathan, 42, presents looking anxious and in considerable pain. A year ago, while moving furniture, he experienced sudden piercing mid-low back pain that radiated down his left leg. The patient had an L4/5 microdiscectomy that appeared at first to relieve radicular symptoms, but the symptoms returned six weeks afterward. His pain intensity at rest is 6 out of 10 on the VAS, but movement brings on back spasms, which causes his pain level to spike to 9 out of 10. Walking and bending at the waist are excruciating, and he finds it hard to find a comfortable position when lying down. He reports that ACET and ibuprofen bring no relief and admits that he would like to receive an ER formulation of oxycodone because he already knows it works for the pain, having occasionally used the same prescription belonging to a friend. Jonathan is now estranged from his parents, both of whom drank to excess and used illegal drugs when he was a child. He reports a history of panic attacks and nightmares ever since his time spent serving in the armed forces. He smokes approximately 30 cigarettes a day. He has no cardiopulmonary, gastrointestinal, endocrine, or neurologic diseases.

1. **How might Jonathan's pain type, intensity, duration and treatments tried inform the creation of a treatment plan for him?**_____

_____

2. **What mental health screening tool(s) would be helpful?**_____

_____

3. **What risk factors for opioid misuse are present and how might they influence treatment choices?**_____

_____

Guidelines and Regulations Governing Long-Term Opioid Therapy

If, after a risk-benefit analysis, a trial of opioid therapy for chronic pain is warranted, HCPs have access to numerous guidelines developed by professional medical societies, states, and federal agencies to assist in setting and executing treatment plans. Common recommendations include: [20,61,77,85,138]

- Start patients on the lowest effective dose
- Conduct UDT at baseline and on follow-up as appropriate
- Check PDMP at baseline and on follow-up as appropriate
- Monitor pain and treatment progress with documentation, using greater vigilance at higher doses
- Pay close attention to drug-drug and drug-disease interactions
- Recognize special risks with fentanyl patches and methadone
- Titrate slowly and cautiously
- Consider using an opioid-specific risk assessment
- Use safe and effective methods for discontinuing opioids (e.g., tapering, making appropriate referrals to substance abuse treatment or other services)

To dispense any controlled substance, including opioids, HCPs must be registered with the DEA. Be aware also that each state may have laws and regulations that govern many aspects of opioid prescribing. Each HCP should check the laws and regulations within the state of practice and take care to comply with all requirements.

Applicable state regulations are evolving rapidly and contain restrictions and directives such as:[139]

- Dose and treatment duration limits
- Expanded PDMPs and new requirements for their use
- Required continuing medical education
- Required written pain treatment agreements
- Required physical exam prior to prescribing
- Required bona fide patient-physician relationship
- Specified timing of follow-up visits and/or UDT
- Presentation of patient identification to a pharmacist prior to receiving opioids
- Medicaid plans requiring single prescriber and single pharmacy for certain high-risk patients

Whenever federal and state law conflict, the more restrictive law applies. The Prescription Drug Abuse Policy System (PDAPS), funded by the National Institute on Drug Abuse, tracks key state laws related to prescription drug abuse here: http://www.pdaps.org/.

The CDC issued has a practice guideline for using opioids to treat patients who have chronic pain and do not have an active malignancy or need palliative or end-of-life care.[61] The guideline defines long-term opioid therapy as use of opioids on most days for greater than three months. Authors of the guideline state that its strictures should not be used to deny clinically appropriate opioid therapy to patients but, rather, to help HCPs in primary care consider all treatment options with an eye to reducing inappropriate opioid use.[140]

Initiating or Continuing Long-Term Opioid Therapy

The HCP may consider a trial of long-term opioid therapy as one therapeutic option if the patient's pain is severe and ongoing or recurs frequently, diminishing function or quality of life, and is unrelieved or likely to be unrelieved by non-opioid therapies.[77] To initiate a trial or continue opioid therapy, the HCP should complete the initial exam and diagnostic procedures and assess pain, mental-health, social, substance, and opioid risk as previously described. A list of items to document in the patient record is shown in Table 7.[20,61,77,85,138,141] Medical records should be kept up-to-date and be legible so as to be easily reviewed.

Informed Consent

Patients started on opioid therapy for chronic pain should be informed of the potential risks and benefits. The most serious risk with any opioid is respiratory depression leading to death. Patients who have never taken opioids or whose medications or doses will be changed should be counseled to expect sedation or other cognitive effects.

An informed consent form should be signed by the HCP and the patient and retained in the medical record. Items recommended in informed consent include:[20,77,141]

- Potential risks and benefits of opioid therapy
- Risks of OUD, overdose, and death even at prescribed doses
- That evidence is limited for benefit of opioids in chronic noncancer pain

Table 7. Items to Perform and Document in the Patient Record When Prescribing Opioid Therapy for Chronic Pain[20,61,77,85,138,141]

1. Signed informed consent
2. Signed opioid treatment agreement(s)
3. Pain and medical history
   - Chief complaint
   - Treatments tried and patient response
   - Past laboratory, diagnostic, and imaging results
   - Comorbid conditions (e.g., medical, substance-use, psychiatric, mood, sleep)
   - Social history (e.g., employment, marital, family status, substance use)
   - Pregnancy status or intent, contraceptive use
4. Results of physical exam and new diagnostic and imaging tests
   - Review of systems
   - Pain intensity and level of functioning
   - One or more indications for opioid treatment
   - Objective disease/diagnostic markers
5. Results of opioid risk assessment prior to prescribing opioids
   - Clinical interview or any screening instruments
   - Personal history of SUD, mental health disorder
   - Family history of SUD, mental health disorder
   - Co-management or treatment referral for patients at risk for SUD
   - Treatment or referral for patients with active OUD
   - Treatment or referral for patients with undiagnosed depression, anxiety, other mental health disorders
6. Treatment goals for pain relief, function, quality of life
7. Treatments provided
   - With risk-benefit analysis after considering available nonpharmacologic and non-opioid pharmacologic op&ons
   - All medications prescribed (including the date, type, dose, and quantity)
   - All prescription orders for opioids and other controlled substances whether written or telephoned
8. Prescription of naloxone, if provided, and rationale
9. Results of ongoing monitoring toward pain management and functional goals

SUD = substance-use disorder OUD = opioid-use disorder; PDMP = prescription drug-monitoring programs; UDT = urine drug testing

- A mention of nonpharmacologic and non-opioid therapeutic options for pain treatment
- Potential short- and long-term side effects, such as cognitive impairment and constipation
- The likelihood that tolerance and physical dependence will develop
- Risks of drug interactions
- Risks of impaired motor skills affecting driving, operating machinery, and other tasks
- Signs and symptoms of overdose
- Risks when combining opioids with other CNS-depressants, including benzodiazepines and alcohol
- The importance of the patient disclosing all medications and supplements
- How to handle missed doses
- Any important product-specific risks, such as the dangers of chewing an ER formulation

Opioid Treatment Agreements

Opioid treatment agreements that spell out patient and HCP expectations and responsibilities are recommended by most opioid guidelines.[77,85] Consider including:[141]

- Treatment goals in terms of pain management, restoration of function, and safety
- Patient's responsibility for safe medication use, such as agreement not to take more than prescribed, alter pills, or combine with alcohol, unauthorized prescriptions, or illicitly-obtained drugs
- Patient's responsibility to obtain prescribed opioids from only one HCP or practice
- Patient's responsibility to fill prescriptions at only one pharmacy
- Patient's agreement to periodic UDT or other drug tests
- Instructions for secure storage and safe disposal of prescribed opioids
- HCP's prescribing policies, including handling of early refills and replacing lost or stolen medications
- Reasons for which opioid therapy may be changed or discontinued, including violation of the treatment agreement
- Statement that treatment may be discontinued without the patient's agreement
- HCPs availability policy, including responsibility to provide care for unforeseen problems and to prescribe scheduled refills
- Education that the patient should not expect complete elimination of pain
- The patient's signature

The forms for informed consent and treatment agreements may be combined into one document and adapted to the HCP's needs and preferences. Examples of informed consent and treatment agreement documents are available online from the New Hampshire Medical Society at https://www.nhms.org/Resources/Opioid-Substance-Related-Resources/Examples-of-opioid-informed-consent-agreement.

Both forms can help facilitate discussions with the patient about ongoing risks and benefits and also provide structure in case difficult conversations become necessary regarding adherence to the treatment regimen. It is advisable to have a strategy to manage opioid misuse by the patient should it occur and to know and discuss with the patient indications for which opioid therapy may be discontinued.

Managing Side Effects

HCPs should expect, prevent, and take steps to manage opioid-related adverse effects. Common opioid side effects with suggested management strategies are listed in Table 8.[77]

Managing Comorbid Disorders

Patients should have psychiatric disorders and psychological symptoms managed in the context of multidisciplinary care. Benzodiazepines may be helpful as second-line agents when used short term to treat the anxiety that arises with pain from injury or hospitalization; however, benzodiazepines are best avoided for long-term use because of their addictive potential, the increased risk for overdose, respiratory depression, and death when co-prescribed with opioids, and the blunting of cognitive and, therefore, coping skills in patients with chronic pain.[1] In 2016, the FDA announced the requirement of boxed warnings with information about serious risks of extreme sleepiness, respiratory depression, coma, and death associated with combining prescription opioids and benzodiazepines.[70]

For chronic mental-health disorders, a combination of medications indicated for the specific condition plus evidence-based psychotherapy, such as CBT, are recommended.[1] SSRIs and SNRIs (and sometimes buspirone) are medications most frequently used for generalized anxiety disorder, which often accompanies chronic pain.[1] Tricyclic antidepressants are sometimes used for panic disorder, but SSRIs, because of their lower side effect profile, are generally considered safest and most effective.[1] Recommended medications for PTSD include venlafaxine ER and prazosin.[1] When comorbid anxiety disorders are severe, psychiatric consultation to establish medication regimen is recommended.[1] In milder cases, no medication may be necessary if adequate behavioral and other nonpharmacologic treatments are helpful.

In general, opioid therapy in patients with untreated OUD is unlikely to achieve therapeutic aims, and initiating it is not recommended.[20] HCPs may consider or continue opioids for patients with chronic pain and histories of drug abuse and psychiatric issues only if they are able to implement more frequent and stringent monitoring parameters.[61]

Table 8. Common Opioid Side Effects and Suggested Management Strategies	
Side Effect	**Management**
Respiratory depression	Screen for sleep apnea Avoid sedatives, benzodiazepines, barbiturates, and alcohol
Constipation	Increase fiber and fluids; start prophylactic laxative treatment, particularly in older patients
Nausea or vomiting	Antiemetic therapy; symptoms tend to diminish
Hormonal deficiencies	Screen symptomatic patients (fatigue, sexual dysfunction
Sedation, mental clouding	Counsel as to home, work and driving safety, and concomitant CNS-depressant risks; symptoms tend to diminish
Pruritis	Treatments largely anecdotal (may include reducing dose, changing medication)
Hyperalgesia	Reduce dose or change medication

In such situations, HCPs should strongly consider consultation and co-management with a pain, mental-health, or addiction specialist or else refer the patient for specialist management.[61,77] Prescription of opioids may not be appropriate until the comorbidity has been addressed.[77]

For patients exhibiting active OUD who are already on opioids, oftentimes at high doses, HCPs should provide or refer for addiction management and treatment with medications such as buprenorphine or methadone via an opioid treatment program.[72]

Treatment of pain with full agonist opioids in patients with OUD would need a careful evaluation of the risks versus benefits to determine management. It is unlikely that a patient with OUD and pain will have adequate pain control in the absence of treatment of OUD.[20] Taper of opioids may be considered in addition to initiation of OUD treatment.

Sudden discontinuation or tapering of opioids in the absence of treatment of OUD with buprenorphine or methadone will put patients with OUD at risk for serious adverse outcomes (see subsequent sections on tapering opioids and managing OUD).[15,16,72]

Dosing and Titration Considerations

Opioids are best when used at the lowest effective dose and combined with non-medication and/or non-opioid medication modalities of treatment.[61,77] When opioids are initiated, the goal is to select the lowest effective dose for shortest duration possible to achieve therapeutic goals.[19,61] The risk of overdose increases with the dose, but the therapeutic window varies considerably from patient to patient.

Various opioid products, delivery systems, and formulations are available to maximize analgesia and minimize or prevent adverse effects. For outpatient chronic pain management, opioids are typically administrated through the oral, transmucosal, and transdermal routes. Each medication has advantages and disadvantages and safety concerns, some of which are intrinsic to all opioids and some of which are specific the route or formulation.

In pain management, IR/SA opioids, are indicated for pain severe enough to need opioid treatment and for which non-opioid treatments are ineffective or not tolerated.[69] These short-acting opioids are preferred and considered safer when initiating a therapeutic trial of opioids and are often prescribed for use as needed every 4 to 6 hours.[69,77] Commonly prescribed IR/SA opioids include morphine, hydromorphone, oxymorphone, codeine, fentanyl, hydrocodone, and oxycodone.[142] Codeine, hydrocodone, and oxycodone are also available in combination with ACET or an NSAID, which limit daily dose due to risk for liver and GI toxic effects.[142] Patients with no or limited exposure to opioids should be initiated at the lowest available dose and titrated slowly to minimize adverse effects.[77] Dual-mechanism opioids may control pain with less opioid, and opioid-sparing techniques, such as combining therapeutics should be considered.

If patients require long-term maintenance and pain is severe enough to require around-the-clock analgesia that is not adequately relieved by IR/SA opioids or other therapies, consider a transition to ER/LA opioids with scheduled dosing.[143] ER/LA opioids are primarily intended to be taken once or twice a day, are not indicated for acute pain, and are for use only in patients who are already tolerant to opioids.[68] It is critical also that HCPs be aware that all transdermal and transmucosal fentanyl and hydromorphone ER products are for use only in opioid-tolerant patients and never for acute or short-term pain.[68] Adult patients are considered opioid tolerant if they have received the following dosages of opioids (or equianalgesic dosages of other opioids) for at least one week:[61,68]

- 60 mg daily of oral morphine
- 25 mcg per hour of transdermal fentanyl
- 30 mg daily of oral oxycodone
- 8 mg daily of oral hydromorphone
- 25 mg daily of oral oxymorphone

Product information for individual formulations contain guidance on degree of opioid tolerance necessary for administration and minimum titration intervals.

IR/SA opioids are sometimes used for severe exacerbations of pain (i.e., "breakthrough pain") that occur against a background of chronic pain that is being treated with ER/LA opioids. This practice has support but is controversial in chronic noncancer pain, because the rapid-onset medications used as rescue medications may increase risk for misuse.[77]

Because patient response varies, titrating to a therapeutic dose should be individualized with close attention to efficacy, tolerability, and presence of adverse effects. The CDC recommends reassessing risk vs. benefit at ≥50 MME per day, avoiding increasing dosages to ≥90 MME per day, or carefully considering the rationale.[61] Authors of the CDC guideline subsequently clarified that the guideline does not support sudden dismissal of patients or hard limits on dosage and treatment durations.[15] These circumstances particularly affect patients who are already receiving long-term opioid therapy and who seek continuation of care after losing access elsewhere.[144] It must be reemphasized that recommended threshold doses do not remove the necessity of exercising caution at any dose or the importance of individualizing the dose.

Particular care is essential, not only during opioid dose initiation but also whenever doses are increased, changed to a different opioid, or when CNS-depressant medications are added to the regimen. Patients should be monitored carefully, particularly within 24 to 72 hours of opioid initiation or upward titration. Studies show that patients are particularly vulnerable to respiratory depression at these times.[119,120]

HCPs should consider opioid initiation a trial, discuss with the patient the risks and benefits of continuing opioid therapy beyond 90 days,[19] and, if opioids are continued, reevaluate the treatment plan at least every three months. Patients who require repeated dose escalations to achieve sufficient pain relief should be reevaluated for the cause, and the risk-to-harm benefit of long-term opioid therapy should be reconsidered.[77]

Opioid Rotation

A patient who suffers inadequate analgesia or intolerable side effects from one opioid may do better with a different opioid.[73] Because mu-agonists produce varied effects, switching a patient to a different medication may allow for pain control at a lowered dose. Care must be taken during the switch, because tolerance to a particular opioid does not translate to tolerance to another, a concept known as incomplete cross-tolerance. Patients should be monitored especially closely during any dose or formulation changes.

Equianalgesic dosing tables, conversion charts, and calculators allow for the conversion of any opioid dose to the standard value of morphine (i.e., MME).[145] These tables have limitations because the supporting studies were conducted on single doses in patients with limited opioid exposure and did not report on dosing over time.[146] Therefore, experts have advised HCPs to use the equianalgesic dosing tables only as a starting point for opioid rotation, then reduce the dose (≥25% to 50% is advised, more with methadone) when converting to the new opioid.[77] A greater reduction is advised in patient who are older or medically frail. A 75% to 90% reduction[147] or considering the patient opioid naïve is advised for rotating to methadone followed by careful monitoring.[77] Conversions to transdermal routes of fentanyl and buprenorphine require special considerations, and HCPs should closely follow instructions in the prescribing information.

Naloxone Prescription

Naloxone can be used to save lives during overdose from a prescribed or illicit opioid, and its presence increases safety for the patient and others who live in or visit the home.[61] Strong evidence shows that providing naloxone to patients reduces opioid-related emergency-department visits.[93]

Take-home naloxone can be easily prescribed and is generally recommended for all patients who receive an opioid prescription. It is particularly recommended with the presence of opioid overdose risk factors, such as history of overdose, history of SUD, clinical depression, opioid dosages ≥50 MME/day, concurrent benzodiazepine use,[61] or with evidence of increased risk by other measures. Two easily administered products are an auto-injection device and a nasal spray that requires no assembly. Patients given naloxone should keep it available at all times.[119]

Naloxone administration can cause withdrawal symptoms, and people who have been administered it should have follow-up medical care. Laws vary by state regarding immunity for physicians or laypeople administering naloxone and can be checked here: http://www.pdaps.org/datasets/laws-regulating-administration-of-naloxone-1501695139.

Patients and their caregivers and other family members should be instructed on the signs of overdose and counseled to do the following if an opioid overdose is suspected:[148]

- Call 911 immediately
- Administer naloxone if available
- Try to keep the person awake and breathing
- Lay the person on their side to prevent choking
- Stay with the person until emergency workers arrive

Signs of an opioid overdose include:[76,148]

- Small, constricted "pinpoint pupils"
- Sedation or loss of consciousness
- Slow, shallow breathing
- Choking or gurgling sounds
- Limp body
- Pale, blue, or cold skin
- Snoring heavily and cannot be awakened
- Periods of ataxic (irregular) or other sleep-disordered breathing
- Trouble breathing
- Dizziness, confusion or heart palpitations

Periodic Monitoring of Long-Term Opioid Therapy

Follow-up with patients being treated with opioids is aimed at preventing potential misuse and tracking progress toward goals of pain control and function. Items to evaluate and document include analgesia, daily activities, adverse effects, aberrant drug-related behaviors, cognition, function, and quality of life. Similarly, patients should be reassessed for the development of tolerance and consideration of adjunctive therapies, opioid rotation, tapering, or discontinuation.[1] Tools available to assist with frequent reassessment and documentation include the Pain Assessment and Documentation Tool[149] and the COMM.[134] Ongoing periodic monitoring should incorporate checks of the PDMP and UDT.[137] When counseling patients, it is best to present UDT, PDMP data, and other monitoring measures to patients as a routine, consensual part of medical care using nonjudgmental language.

The CDC guideline states that patients on opioid therapy should be reevaluated within one-to-four weeks of initiation or dosage change and at least every three months thereafter to ensure benefits outweigh risks.[61] Monitoring measures should be ongoing with every patient prescribed opioid therapy.[20] Patients with more comorbidities or higher misuse risk require more stringent monitoring measures and more frequent follow-up than patients with less risk for harm.[19] Some expert guidance recommends using risk stratification to set clinic visit frequency and other monitoring measures as determined by patient risk category (low, moderate, or high risk) during initial screening and clinical follow-up.[77]

The recommended frequency for periodic review of PDMP data ranges from every prescription to every three months.[61] A consensus-based recommendation for UDT frequency is to test every patient at least once annually and higher-risk patients from two-to-three times annually.[137] It is very important to check local and state regulations and the recommendations of state medical boards in the area of practice, as many of these bodies set expectations for the timing and other particulars regarding UDT and PDMP checks.

Interpreting UDT results requires caution as the tests have limitations.[61] These include:[137]

- Cross-reactivity with other drugs or substances
- Potential for false positives (e.g., poppy seeds positive for opiates)
- Potential for false negatives
- Variable drug metabolism
- Laboratory error

Unexpected results, such as the absence of prescribed medications that could indicate diversion, should be discussed with the patient and documented in the record along with plans to address the results.

Reassessment of any comorbid mental health disorders is also part of ongoing opioid therapy. Tools used for initial assessment of anxiety, depression, and somatic symptoms may also be used for monitoring of these conditions and reevaluating the treatment plan.[150]

Seeking Expert Referrals

Knowing hen to seek specialist care is part of treatment with opioids. In general, the HCP should consult with a pain, addiction, or mental-health specialist or refer the patient for specialist care whenever:

- Pain continues to worsens with treatment
- OUD is suspected or identified
- Worsening of any mental health disorder is observed, including any SUD

Uncontrolled or increasing pain severity despite attempts to optimize the medication regimen and in the absence of a clear explanation is a signal that pain specialist consultation or referral is advisable.

In the presence of ongoing or severe behaviors suggestive of opioid misuse, HCPs should consider that patient may be suffering from OUD or other substance-use or mental-health disorders. When an active OUD or a recent OUD history is present, HCPs should strongly consider referral for medication treatment of addiction (unless this is provided in your clinic), specialist pain management, and/or tapering opioids and managing pain with non-opioid therapies.[61]

Criteria of an OUD are described later in this activity. Signs and symptoms seen in a clinical scenario include:[151]

- Taking opioids compulsively and long term for no legitimate medical purpose
- If pain is present, taking opioids in excess of prescription
- Obtaining opioids from unauthorized sources
- Falsifying or exaggerating medical problems to receive opioids
- Significant tolerance and physical dependence (although these may also occur in patients without OUD)
- Conditioned responses of craving that persist after cessation

Other life circumstances that may accompany OUD but are not always seen include:[151]

- Marital problems, including divorce
- Unemployment and irregular employment
- Financial insecurity
- History of drug-related crimes

SUDs involving alcohol or any other drug may threaten the success of opioid therapy and introduce safety risks. SUD should be suspected when the recurrent use of alcohol or drugs causes clinically significant impairment, including health problems, disability, and failure to meet major responsibilities at work, school, or home. The coexistence of both a mental health and an SUD is referred to as co-occurring disorders. The National Institute for Mental Health's Mental Health Information website has information about specific mental conditions and disorders as well as their symptoms: https://www.nimh.nih.gov/health/topics/. The presence of a psychiatric or substance-use condition does not mean the patient is not experiencing real pain. The many contributing factors from the biological, psychological, and social domains as well as chronic pain's adverse impact on relationships, work, sleep, function, overall health, and quality of life explain why a comprehensive approach to pain management is optimal.[14] These complexities also explain why patients often respond better to a combination of therapeutic modalities rather than a unimodal medication regimen.

Tapering

Before initiating opioid therapy, HCPs should have an exit strategy in place to humanely taper opioids whether the goal is dose reduction or to discontinue opioid therapy. Indications for discontinuing opioid therapy may include:[72]

- Failure to achieve sufficient analgesia
- Intolerable side effects
- Resolution of pain
- Development of OUD or serious misuse
- Higher doses without evidence of benefit
- Presence or warning signs of an impending serious event (e.g., confusion, sedation, slurred speech)
- Concurrent medications (e.g., benzodiazepines) that increase risk for a serious outcome
- Concurrent medical condition(s) (e.g., lung disease, sleep apnea, liver disease, kidney disease, fall risk, advanced age) that increase risk for a serious outcome
- A pattern of ongoing failure to adhere to the treatment plan to which the patient agreed

Signs of serious nonadherence that may indicate opioids are unsafe for the patient include:[77]

- Repeatedly increasing dose without HCP knowledge
- Sharing medications
- Unapproved opioid use
- Use of illicit drugs
- Obtaining opioids from unauthorized sources
- Prescription forgery
- Multiple episodes of losing prescriptions
- Polysubstance use

The CDC suggests evaluating new patients currently on >90 mg MMD daily opioid dose or whenever risks outweigh benefits for tapering protocol,[61] while the VA/DoD practice guideline recommends a comprehensive reassessment that recognizes the risks of the high dose.[20] However, one must beware of abrupt opioid discontinuation and know that treatment is individualized.[1,15-17,20] The CDC guideline is meant to advise HCPs to avoid increasing doses above 90 mg MME daily but is not meant to circumscribe individualizing treatment or to justify abrupt reduction from high doses.[72] Nor is the guideline meant to justify reducing or discontinuing opioids that may be medically indicated and when benefits outweigh risks.[72]

Patients who are candidates for taper should be treated with alternatives to opioid therapy for pain. HCPs should avoid dismissing patients from care and should ensure whenever possible that patients continue to receive coordinated care.[72] Referral should include, as indicated, treatment of OUD or management of psychiatric illnesses.[119] In an outpatient setting, taper should be done so as to avoid opioid withdrawal in physically-dependent patients. Taper may be accomplished in a detox setting if the patient is unable to reduce opioid dose.

An expert consensus guideline offered the following recommendations regarding tapering opioids:[20]

- Evaluate comorbidities, the patient's psychological condition, and other relevant factors before beginning the taper
- Educate the patient and family about the taper protocol
- Manage withdrawal symptoms (e.g., nausea, diarrhea, muscle pain, myoclonus) using non-opioid analgesics and adjuvant agents
- For complicated withdrawal symptoms, refer the patient to a pain specialist or chemical dependency center
- Refer for counseling or other support during the taper if there are significant behavioral issues

Diversion of opioids or other controlled substances is a contraindication for continuing opioid therapy.[20] With confirmed diversion, the best practice is to monitor for withdrawal symptoms, offering necessary support and treatment of SUD, if present.[20]

There is no one established taper rate that will work best for every patient.[1,15-17,20] Certain characteristics will influence the recommended speed of tapering. These include opioid dose, duration of therapy, type of opioid formulation, and co-occurring psychiatric, medical, and substance-use conditions.[20] Various rates have been studied or recommended by experts:

- The CDC recommended 10% per week reduction as a starting point.[152]
- A more recent HHS guide suggested individualized tapering plans that range from slower tapers of 10% per month (or slower) to faster tapers of 10% per week until 30% of the original dose is reached, followed by 10% weekly reductions of the remaining dose.[72]
- The VA/DoD practice guideline suggests 5% to 20% reduction every four weeks, individualizing according to patient need (e.g., some patients may need or tolerate a faster taper when risks are too high, while patients on high doses require a very slow taper).[20]
- The HHS guide allows for rapid tapers (e.g., over two-to-three weeks) when risks of continuing the opioid outweigh the risks of a rapid taper (e.g., in the case of a severe adverse event such as overdose) and further warns that ultrarapid detoxification under anesthesia is associated with substantial risks and should not be used.[72]

A principle to remember is that slow tapers may require several months or years and are more appropriate than faster tapers for patients who have been receiving prolonged opioid therapy.[72] Rapid reduction of opioid doses should occur only if there is imminent danger to the patient from continuing doses (such as an overdose event at the current dose, medical complications, or dangerous behaviors such as injecting opioids), or in cases in which it is discovered the individual is obtaining pills to divert.[61,144]

Tapering works best when it is collaborative between the HCP and the patient, when tapering is slow and careful, when support and close monitoring are offered, and when comorbidities such as depression, anxiety, and insomnia are concurrently addressed.[144] It is helpful to slow or to pause and restart tapering at times. There are serious risks to noncollaborative tapering in patients who have been prescribed opioids for a long period and have physical dependence, including acute withdrawal, pain exacerbation, anxiety, depression, suicidal ideation, self-harm, ruptured trust, and patients seeking opioids from high-risk sources.[72] Include patients in discussions of taper planning and take time to gain patient buy-in to the plan whenever safety allows.

It is of paramount importance to address opioid withdrawal symptoms (Table 9).[144] Early withdrawal symptoms (e.g., diarrhea and cramping, anxiety, restlessness, sweating, yawning, muscle aches) usually resolve after 5-10 days but can take longer.[72] Other post-acute withdrawal symptoms (e.g., dysphoria, insomnia, irritability) can take weeks or months to resolve.[72] Recommended oral medications to manage withdrawal symptoms (particularly for faster tapers) include alpha-2 agonists for autonomic symptoms such as sweating and tachycardia and symptomatic medications for muscle aches, insomnia, nausea, cramping, and diarrhea.[72]

Table 9. Common Opioid Withdrawal Symptoms[144]	
Physical symptoms	Tremor Diaphoresis Agitation Insomnia Myoclonus Diffuse pain/hyperalgesia Hyperthermia Hypertension Cramping/diarrhea Pupillary dilation Piloerection Release of stress hormones Pain increase
Affective symptoms	Dysphoria Anhedonia Anxiety Depression Hopelessness/suicidal ideation

Follow-up and behavioral health support is very important during tapering. HCPs should acknowledge patient fears of pain, stigma, withdrawal, and abandonment while reassuring them that many patients have improved function after tapering, although the pain might be worse at first.[72,93] This is a time to collaborate with mental-health and other specialists and to watch closely for signs of OUD, anxiety, depression, and suicidal ideation. At least weekly follow-up has been used in successful tapers.[72]

Buprenorphine or Slow Taper in Select Patients

In some patients on long-term opioid therapy, even on higher-than-recommended doses, with demonstrated benefit and no evident adverse effects, aberrant behavior, or major risks, taper may not be the best course of action.[144] Reports of harms after involuntary opioid discontinuation include overdoses, termination of care, emergent hospital or emergency department visits, and suicidal ideation or behavior.[144] Though other patient factors may also contribute to these behaviors, opioid stoppage in such patients, particularly when abrupt or nonconsensual, may put them at risk for poor outcomes.[144]

Patients with worsened pain and function despite high daily opioid doses may exhibit a poor response to taper, whether or not OUD criteria are met, and may benefit from transitioning to buprenorphine.[72] Buccal and cutaneous patches of low-dose buprenorphine are FDA-approved for the treatment of pain, and buprenorphine/naloxone has been used off-label as an analgesic for chronic pain.[144] Buprenorphine has safety advantages over full mu agonists because respiratory depression tends to plateau as dose increases, and it is also less subject to dose escalation. Use of buprenorphine/naloxone to treat OUD no longer requires specific training, but a waiver from the Drug Enforcement Administration (DEA) is required to prescribe it. Practitioners are encouraged to receive training prior to use and there are new, short trainings that are freely available (see the following link: https://elearning.asam.org/products/buprenorphine-mini-course-building-on-federal-prescribing-guidance#tab-product_tab_overview.)

Transitioning from a full agonist opioid to the partial opioid agonist of buprenorphine requires careful attention to timing and may best be accomplished with consulting with an HCP experienced in its use. See the following link for support: https://pcssnow.org/.

Check the prescribing information for safe induction practice,[153] and consider the following safety principles with buprenorphine analgesia treatment as endorsed by an expert panel:[144]

- Buprenorphine may produce acute opioid withdrawal in patients on full mu agonists
- Patients discontinue all opioids the night before initiation (time depending on duration of action)
- After mild withdrawal is present, initiate 2-4 mg (repeated at two-hour intervals, if well tolerated, until withdrawal symptoms resolve)
- Typically, 4-8 mg will be needed the first day
- Reevaluate on day two and increase dose if needed
- Total dose given on day two can then be prescribed as the daily dose
- Unlike treatment for OUD, buprenorphine for analgesia should be given in three-to-four daily doses

Other patients with poor pain control and function who do not tolerate taper well may do better with a very slow taper over many months or even years.[144] Tapering decision points are shown in the following flow chart with the reminder that follow-up timing should be frequent and individualized (Figure 4).[72] Patients who continue on high-dose or otherwise high-risk regimens should be monitored, provided with overdose education and naloxone, and periodically encouraged toward appropriate therapeutic changes.[72]

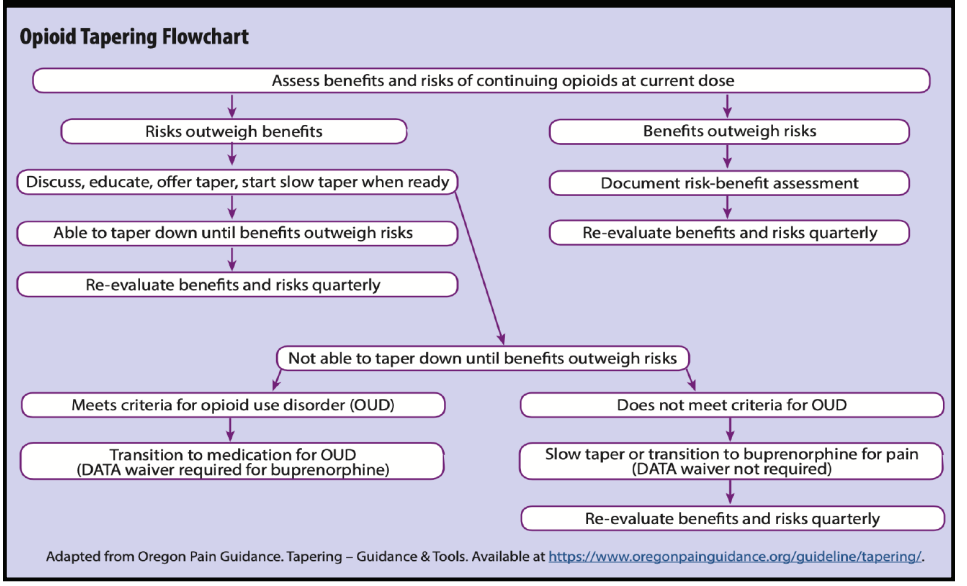
BEFORE MOVING ONTO THE NEXT SECTION, PLEASE COMPLETE CASE STUDY 2 ON THE NEXT PAGE.

Managing OUD

Methadone and buprenorphine are used to treat OUD, a process known as medication treatment for OUD (MOUD) when combined with behavioral therapy.[69] Buprenorphine works by suppressing and reducing opioid cravings. Methadone reduces cravings and withdrawal and also blunts the effects of opioids. Buprenorphine is widely used and encouraged for treating patients with OUD.[1,18] One reason is buprenorphine's antagonistic action at the kappa receptor, as this effect is associated with reducing opioid withdrawal symptoms along with helping to attenuate anxiety and depression.[1]

HCPs should treat OUD with buprenorphine/naloxone if authorized by the DEA Drug Addiction Treatment Act of 2000 waiver or should refer the patient for addiction treatment.[144] Recent practice guidelines released by the Substance Abuse and Mental Health Services Administration within HHS are available here: https://www.samhsa.gov/newsroom/press-announcements/202104270930. Approaching OUD as a chronic illness can help patients to stabilize, achieve remission of symptoms, and establish and maintain recovery.[18]

Figure 4.



Adapted from Oregon Pain Guidance. Tapering – Guidance & Tools. Available at https://www.oregonpainguidance.org/guideline/tapering/.

Case Study 2

Instructions: Spend 5–10 minutes reviewing the case below and considering the questions that follow.

Giorgio, 62, has a long history of chronic pain in his back from degenerative disc disease. He has had three surgeries and tried trigger point injections and multiple medication regimens that include NSAIDs and gabapentinoids before being prescribed oxycodone for pain. He began to request higher oxycodone doses, citing difficulty sleeping and inability to function. He began to visit the clinic without an appointment, demanding opioids and behaving in an agitated and aggressive manner toward clinic staff. He was transitioned to methadone at 30 mg daily. The methadone relieved his pain at first but analgesia began to wane and his dose was increased until it reached 120 mg daily. As his pain continued to worsen, his HCP refused to raise his methadone dose any higher. Giorgio has a history of depression but does not take antidepressants. He can no longer work because of the pain, which he describes as at least a constant 9/10 on the numerical pain score. He is restless and finds it difficult to sit still during examination. A routine UDT turned up evidence of methamphetamine. During follow-up of the result, he admits to seeking out the street drug and also to procuring a few doses of heroin. He has a history of alcohol-use disorder that was in remission for many years but admits to recent relapse.

1. **What opioid risk factors and clinical signs and symptoms can be observed in Giorgio?**_____

2. **How might the Opioid Tapering Flowchart shown Figure 4 be used to evaluate and treat this patient?**_____

3. **What type of specialty referral is advisable for Giorgio?**_____

Patients with OUD should have access to mental health services, medical care, and addiction counseling to supplement treatment with medication.[18] Individualized psychosocial supports may include supportive counseling, recovery coaching, recovery support services, and other services that may be needed by particular patients.

Patients who present with or develop OUD or mental health disorders or both and who also have persistent pain require multidisciplinary care.[1] Patients with co-occurring pain and OUD should be offered MOUD.[18,19]

For any population with trouble accessing treatment for OUD, including poorer urban areas and rural areas with limited treatment options, expanding the number of qualified HCPs able to treat OUD with buprenorphine in an office-based setting leads to more ready diagnosis and treatment.

Because OUD medication is best combined with evidence-based psychological and behavioral therapies, the growing popularity and feasibility of accessing telehealth sessions is another possible means of expanding access to currently underserved communities.

Opioids and Concurrent Cannabis

Some patients who are taking opioids for pain are also using cannabis concurrently. However, synthesis of the data has been incomplete to guide clinical choices, and the short- and long-term health and safety effects have remained elusive. There are some data suggesting those who take medical cannabis are similar demographically to those who use cannabis recreationally.[154]

A prospective cohort study of patients with musculoskeletal pain who are also on a stable dose of opioids was conducted to compare those who endorsed past-month cannabis for pain to those who denied any cannabis or illicit drug use.[155] Of 17% who endorsed past-month cannabis use for pain, 31% had a current medical cannabis card, and 66% reported that cannabis was helpful for reducing pain. Those who used cannabis for pain had higher rates of nicotine use, risk for prescription opioid misuse, and hazardous opioid use. No difference between groups were found in opioid dose, pain intensity, pain interference, or depression severity.

The most common route of administration is smoking, despite risks of pulmonary effects. Some evidence suggests vaporization may be safer in this regard, although other research notes similar exposure as smoking to carbon monoxide and other respiratory toxins.[156] Other delivery options including edibles and extracts.

Patients may develop cannabis-use disorder (CUD) and be unable to stop use on their own even though it is interfering with their health and function. Signs of CUD include:[155]

- Using a larger quantity or over a longer duration than intended
- Unsuccessful attempts to limit or quit
- Significant amounts of time spent obtaining cannabis
- Cravings
- School or occupational impairment
- Social or interpersonal impairment
- Reduction of social, occupational, or recreational activities
- Recurrent use in physically harmful situations
- Continued use despite recurrent physical or psychological harms
- Tolerance
- Withdrawal

Because some patients who are taking opioids will elect to use cannabis, HCPs should be aware of certain clinical recommendations:[156]

- Keep current with relevant federal, state, and institutional policies and laws
- Establish goals of care for cannabis use
- Screen for signs of misuse, CUD, and diversion
- Counsel patients on harms and risks on the basis of symptoms, condition, and comorbidities
- Advise on routes of administration using current evidence base
- Continually monitor similarly to opioids (informed consent, written agreement, regular follow-up, functional status, considering periodic urine testing, symptom severity, and use of other medications or substances)
- Monitor for other harms, including car accidents and falls
- Advise on discontinuation or referral to CUD treatment if pain relief and function goals are not being met without harm

Although not specific to pain therapy, useful measures to screen for CUD include:

- Single question: How often in the past year did you use marijuana (never, less than monthly, monthly, weekly, daily or almost daily)[155]
- The 8-item Cannabis Use Disorders Identification Test-Revised (CUDIT-R)[157]
- Comprehensive Marijuana Motives Measure[158]

The Basics of Addiction Medicine

Definitions and terms used to discuss addiction have evolved over time. Certain phrasing that is potentially stigmatizing has fallen out of usage, and more accurate terminology has been introduced. For example, patients with SUD, including OUD, should not be referred to as "addicts." The disease of OUD is diagnosed using DSM-5 criteria (Table 10).[92] A minimum of two-to-three criteria are required for a mild SUD diagnosis, while four-to-five is moderate, and six or more is severe;[92,151] OUD is specified if opioids are the substance of use. Addiction, while not a DSM-5 diagnosis, is a frequently used term and typically describes severe SUD. The presence of tolerance and physical dependence does not necessarily mean that an OUD has developed, particularly if the medication is taken as prescribed.

The rewarding effects of drugs occur through dopamine stimulation in the mesolimbic system of the brain.[159] When a drug stimulates the brain's mu opioid receptors, cells in the ventral tegmental area release dopamine into the nucleus accumbens, causing pleasurable feelings.[159] The pharmacokinetics and lipophilicity of the drug and its route of administration influence the speed and amount of dopamine released and thus the degree of reward experienced by the individual. Intravenous and inhalational use speeds onset more than oral ingestion. However, ER/LA opioids can be altered by the individual to produce a rapid onset of action by crushing, chewing, or dissolving in liquids, for example.[68]

Repeated ingestion stimulates the brain's reward system. At the same time, the brain creates conditioned associations and lasting memories that associate reward with environmental cues of drug use. Normally, inhibitory feedback from the prefrontal cortex helps most individuals overcome drives to obtain pleasure through unsafe actions.[159] However, prefrontal cortex inhibitory cues are compromised in people with addictions, and drug use behaviors are driven by a complex combination of both positive and negative reinforcements. Positive reinforcements include the individual's pleasure from using the substance and negative reinforcements include the desire to prevent withdrawal. As tolerance and dependence develop, more drug is necessary to obtain the same reward and prevent withdrawal. The locus coeruleus area of the brain plays an important role in the production or suppression of withdrawal symptoms. When an OUD is present, the compulsion to use opioids repeatedly goes beyond the reward drive. As changes in the brain develop, the person's experience of pleasure diminishes and they engage in the compulsive drug use despite adverse consequences that characterizes OUD.[159]

Conclusions

All HCPs who treat pain with the use of opioids need up-to-date competencies to manage potential opioid-related harms. This includes a familiarity with the full complement of nonpharmacologic and pharmacologic options to create an individualized treatment plan, reserving opioids for when other strategies are not effective.

An optimal multimodal approach to pain management consists of using treatments from one or more clinical disciplines incorporated into comprehensive plan.[1]

For select patients who benefit from opioids long term, HCPs should reduce risk and optimize benefits by patient education, screening of high-risk patients for OUD, continuous monitoring, combining treatments with non-opioid options when indicated, referral and co-management of comorbid conditions, and an exit strategy to ensure careful tapering when indicated. It is important for patient outcomes and for regulatory and legal requirements to document every aspect of opioid therapy within the medical record and to follow all federal, state, and local regulations regarding opioid therapy. HCPs should know the signs and symptoms of OUD and be prepare to treat or refer for treatment with the understanding that medications for OUD are essential to save lives.

Table 10. Criteria for Opioid-Use Disorders from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition[92]

A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:
• Opioids are often taken in larger amounts or over a longer period of time than was intended
• There is a persistent desire or unsuccessful efforts to cut down or control opioid use
• A great deal of time is spent in activities to obtain the opioid, use the opioid, or recover from its effects
• Craving, or a strong desire or urge to use opioids
• Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home
• Continued opioid use despite having persistent or recurrent social or interpersonal problems caused by or exacerbated by the effects of opioids
• Important social, occupational, or recreational activities are given up or reduced because of opioid use
• Recurrent opioid use in situations in which it is physically hazardous
• Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that's likely to have been caused or exacerbated by the substance
• Tolerance,* 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
• Withdrawal,* as manifested by either of the following: a. The characteristic opioid withdrawal syndrome b. The same—or a closely related—substance is taken to relieve or avoid withdrawal symptoms
*This criterion is not met for individuals taking opioids solely under appropriate medical supervision. Severity: mild = 2–3 symptoms; moderate = 4–5 symptoms; severe = 6 or more symptoms.

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BEST PRACTICES FOR TREATING PAIN WITH OPIOID ANALGESICS

Self-Assessment

Choose the best possible answer for each question and mark your answers on the self-assessment answer sheet at the end of this book. There is a required score of 70% or better to receive a certificate of completion.

1. What is one way to reduce the stigma for patients living with chronic pain?

A. Counseling patients in whom opioids are indicated that opioids are appropriate for them.
B. Urging patients to self-manage moderate-to-severe pain.
C. Optimizing use of non-steroidal anti-inflammatory drugs.
D. Ensuring that individuals from minoritized racial and ethnic backgrounds have greater access to opioid therapy.

2. Gabapentin has mild-to-moderate benefit in the treatment of:

A. Insomnia that commonly accompanies chronic pain.
B. Short-term inflammation associated with acute pain caused by injury or surgery.
C. Muscle spasm in low-back pain as an alternative to more sedating medications.
D. Neuropathic pain syndromes.

3. Spinal manipulation has demonstrated improvements in pain and function when used:

A. In combination with opioids in pain lasting longer than 3 months.
B. For chronic tension headache.
C. For fibromyalgia.
D. In patients with chronic neck pain and concomitant opioid-use disorder (OUD).

4. Which is a true statement about factors to record in the patient record?

A. Psychological and social factors should be included as these can contribute to the pain experience.
B. Objective clinical markers for pain must be present before pain treatment is given.
C. The primary objective of pain treatment is to document a reduction in the patient's self-reported pain scale number.
D. Diagnosis of chronic pain is made if pain is continuous.

5. Which of the following tools assess pain, pain interference, functional components, and quality of life, and was created to assess management of chronic pain in primary care settings?

A. McGill Pain Questionnaire (MPQ).
B. Pain, Enjoyment of Life, and General Activity Scale (PEG).
C. Revised Screener and Opioid Assessment for Patients with Pain (SOAPP-R).
D. The Visual Analogue Scale (VAS) combined with the Numerical Rating Scale (NRS).

6. Which is a true statement about screening patients for potential opioid misuse?

A. Only the Drug Abuse Screening Test has been associated with a high degree of predictive accuracy.
B. Brief screening tools are regarded to have clinical utility in diagnosing OUD.
C. Single screening questions may be used.
D. There is no evidence to support screening for risk ahead of opioid prescription.

7. Patients who are already being prescribed opioids for chronic pain who exhibit an active OUD should be:

A. Discontinued immediately from opioids and treated with nonpharmacologic pain therapies.
B. Engaged in collaborative taper and treated or referred for treatment with medications to manage OUD.
C. Tapered rapidly from opioid doses and encouraged to seek psychiatric counseling.
D. Rotated to a dual-mechanism opioid with less misuse potential and sent for detoxification from high-dose opioids.

8. **Which of the following is an example of an opioid-related risk factor appropriately influencing a treatment choice?**
   A. Pain duration lasting longer than 6 months is a contraindication for carisoprodol co-prescribed with opioids.
   B. Patients without previous exposure should be initiated at the lowest possible dose of an extended-release opioid and titrated slowly to minimize adverse effects.
   C. Cardiac toxicities due to QTc prolongation suggest morphine should be carefully evaluated or should not be used.
   D. Take-home naloxone is advised in the presence of concurrent benzodiazepines.

9. **One sign of an active OUD is:**
   A. Craving that persists after cessation.
   B. Combining opioids with alcohol.
   C. Persistent failure of analgesia despite optimal doses.
   D. Chronic insomnia with opioid therapy for pain.

10. **Which of the following statements is true regarding a diagnosis of OUD using DSM-5 criteria?**
   A. A minimum of four criteria are required for a mild OUD diagnosis.
   B. The preferred term for problematic opioid usage that does not meet criteria for OUD is “abuse”.
   C. The presence of tolerance and physical dependence does not necessarily mean that an OUD has developed.
   D. Patients cannot develop an OUD if they take medication as prescribed.

NOTES

EVIDENCE-BASED GUIDANCE ON PRESCRIBING CONTROLLED SUBSTANCES

COURSE DATES:	MAXIMUM CREDITS:	FORMAT:
Release Date: 10/2021 Exp. Date: 9/2024	3 *AMA PRA Category 1 Credits*™	Enduring Material (Self Study)

TARGET AUDIENCE

This course is designed for all physicians and health care providers involved in the treatment and monitoring of patients prescribed controlled substances.

HOW TO RECEIVE CREDIT:

- Read the course materials.
- Complete the self-assessment questions at the end. A score of 70% is required.
- Return your customer information/ answer sheet, evaluation, and payment to InforMed by mail, phone, fax or complete online at program website.

COURSE OBJECTIVE

The purpose of this course is to educate health care providers about the requirements of the Controlled Substances Act and safe prescribing practices for both opioid and non-opioid controlled substances. In addition, some of the medical conditions for which controlled substances are most commonly prescribed will be reviewed, along with recommendations for responsible management of these conditions with specific controlled substances.

LEARNING OBJECTIVES

Completion of this course will better enable the course participant to:

1. Discuss optimal treatment regimens when using controlled substances for common medical conditions.
2. Identify preventions for misuse/diversion and safeguards for controlled substances.
3. Understand controlled substance regulations and tools for appropriate prescribing.
4. Discuss diagnosis of OUD, optimal treatments, and when to refer to appropriate specialists.

ACCREDITATION STATEMENT

InforMed is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

DESIGNATION STATEMENT

InforMed designates this enduring material for a maximum of 3 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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DISCLOSURE OF INTEREST

In accordance with the ACCME Standards for Commercial Support of CME, InforMed implemented mechanisms, prior to the planning and implementation of this CME activity, to identify and resolve conflicts of interest for all individuals in a position to control content of this CME activity.

COURSE SATISFIES

SPECIAL DESIGNATION

This course satisfies three (3) hours on prescribing and monitoring of controlled substances.

The South Carolina Board of Medical Examiners requires physicians (MD/DO) to complete two (2) hours on safe prescribing and monitoring of controlled substances as a condition of renewal. Physician assistants with controlled substance prescriptive authority must complete four (4) hours on safe prescribing and monitoring of controlled substances as a condition of renewal. The South Carolina Board of Podiatry Examiners requires podiatrists authorized to prescribe controlled substances to complete two (2) hours on safe prescribing and monitoring of controlled substances as a condition of renewal.

FACULTY/PLANNING COMMITTEE DISCLOSURE

The following faculty and/or planning committee members have indicated they have no relationship(s) with industry to disclose relative to the content of this CME activity:

- Beth Dove
- Michael Brooks

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- Melissa B. Weimer, DO, MCR, FASAM has received honoraria from Path CCM, Inc. and CVS Health.

STAFF AND CONTENT REVIEWERS

InforMed staff, input committee and all content validation reviewers involved with this activity have reported no relevant financial relationships with commercial interests.

DISCLAIMER

Introduction

Controlled substances (CS) are used to treat many medical conditions but are associated with risks to patients and society.[1-4] Research suggests that the potential for misuse of non-opioid medications is under appreciated by heath care providers (HCPs).[5-8] Although most overdose deaths still involve opioids,[9] polysubstance involvement is on the rise and includes prescription stimulants, benzodiazepines, and sedative-hypnotics.[6-8] Misuse of any prescription drug is a serious problem, and that includes opioid and non-opioid CS.[1-4,10]

Actions aimed at containing the societal opioid crisis have paralleled increased prescription rates for non-opioid CS,[11,12] some of which are recommended as first-line agents for pain treatment.[13] Despite these efforts, reductions in opioid prescriptions[14] have not seen a corresponding drop in overdose drug deaths in the United States.[9] At the same time, interest in non-opioid CS has grown: prescriptions for stimulants have risen sharply, and benzodiazepines are among the most commonly prescribed CS (Figure 1).[4] An analysis based on a single commercial insurance provider found a "concerning" 5-fold rise in stimulant use over 15 years (2004-2019).[4]

Furthermore, HCPs are not always using best practices when prescribing CS.[5,15,16] For example, in a survey of certified nurse-midwives in New Mexico with a registration to prescribe CS, approximately 10% never logged into the state prescription drug-monitoring program (PDMP), 40% never ran a self-report, and nearly 30% reported never checking the database for patient alerts.[16] HCPs are also eager to prevent illegal diversion of CS[15] but find it difficult to distinguish diversion from legitimate use.[17,18]

Finally, research indicates that significant barriers still prevent broad access to treatment for opioid-use disorder (OUD), despite strong evidence that treatment with medications approved by the US Food and Drug Administration (FDA) for OUD reduces morbidity and mortality.[15] Fewer than a third of people with OUD receive treatment, and those who do often wait years to begin.[15,19] Additional barriers include stigma, lack of professional education and training related to the evidence base for using medication to treat OUD, and a fragmentary health care system that does not incentivize best care.[15]

To appropriately manage patients while minimizing diversion and misuse, HCPS must stay abreast of the existing and evolving laws, regulations, and policies that govern CS prescribing and to comply with all requirements.[18] To improve patient outcomes and minimize misuse, HCPs should aim to recognize the signs and symptoms of appropriate medical indications for prescribed CS.[5,17,18]

This activity is designed to educate HCPs about the requirements of federal and state law that make up the legal and regulatory framework of CS prescribing. The goal is to facilitate safe, responsible prescribing practices and patient education. Emphasis is on helping HCPs to match CS medication to the appropriate medical condition, reduce risks for substance misuse and diversion, set office policies to comply with regulatory and legal requirements, and increase competencies in recognizing and optimally treating substance-use disorder (SUD) involving CS.

History of Federal Controlled Substances Law

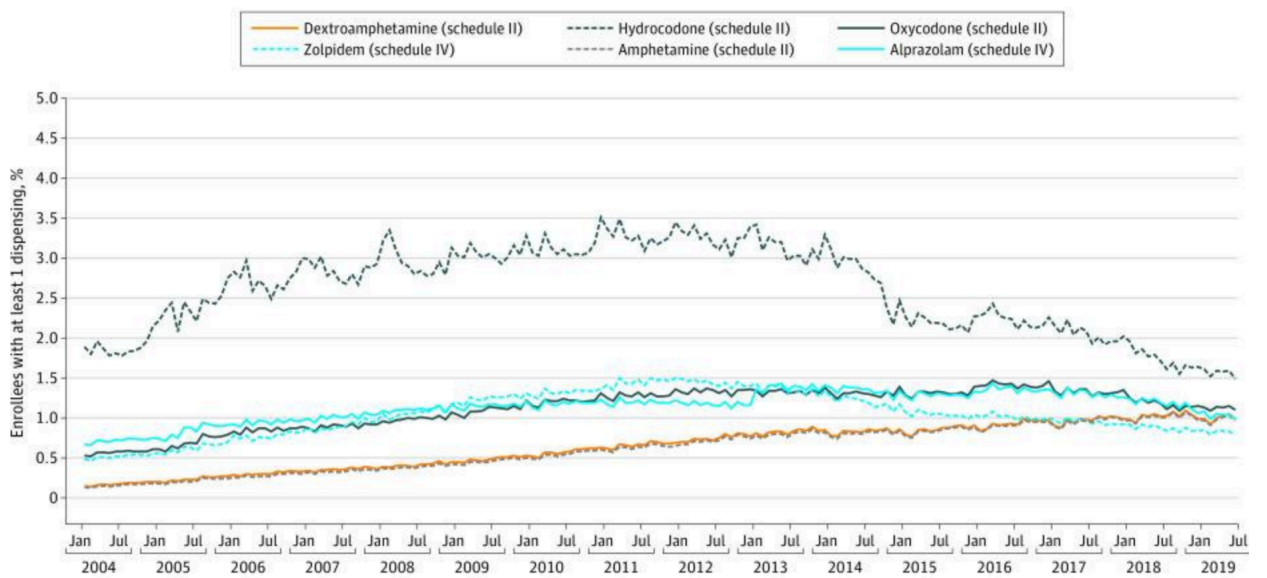
Drugs or medications with the potential for misuse and a high risk of resulting in SUD are strictly controlled by the federal government. The aim is to protect access to drugs with a legitimate medical purpose while preventing the detrimental effects of illegal importation, manufacture, distribution, possession, and improper use.

Federal, state, and local governments generally did not regulate drug distribution or use until the 20th century.[20] In 1914, the Harrison Narcotics Act was passed in response to rising levels of drug use and required importers, manufacturers, and distributors of cocaine and opium to register with the government, keep track of each transaction, and pay a special tax.[20] The United States joined the Single Convention on Narcotic Drugs of 1961, a measure to control international and domestic traffic in narcotics, coca leaf, cocaine, and cannabis.[21] A second treaty, which entered into force in 1976 and was ratified by Congress in 1980, was designed to establish comparable control over stimulants, depressants, and hallucinogens.[21]

Throughout the 20th century, several laws were passed criminalizing drug abuse. In the 1960s, severe penalties fell out of favor as advocates began to support a medical approach to drug misuse, and methadone treatment for OUD became more accepted. However, law enforcement was also a popular deterrent as recreational drug use grew widespread during the 1960s. The culmination of the impetus to stem drug misuse while preserving legitimate use of drugs was the Controlled Substances Act (CSA), which took effect in 1971 and combined regulation of medical practice with enforcement.[20]

The Drug Enforcement Administration (DEA) enforces federal CS laws in all states and territories. In recent decades, the agency's approach to curtailing drug misuse and diversion of pharmaceutical opioids has been to focus on traffickers and doctors who prescribe inappropriately rather than on individuals who illegally obtain opioids.[20] This reflects a shift away from public policies and laws, popular in the 1980s, marked by penalties to hold drug users personally responsible for their illegal drug activity.[21]

Figure 1. Trends for Most Commonly Dispensed Controlled Substances in US Commercially-Insured Adults (January 2004 to June 2019)



*Based on de-identified longitudinal claims data on beneficiaries of a large US employer-sponsored commercial health insurance provider and covers approximately 9 million individuals ages 19 to 64 years in any given month across all 50 states.

Drug Schedules

Today, the CSA regulates manufacture, distribution, and dispensing of CS with specifics laid out in the Code of Federal Regulations (CFR) Title 21, §§1300-1316. Under the CSA, illegal and prescription drugs are classified into 5 schedules according to:[20,21]

- Actual or relative potential for misuse
- Known scientific evidence of pharmacological effects
- Current scientific knowledge of the substance
- History and current pattern of misuse
- Scope, duration, and significance of misuse
- Risk to public health
- Psychic or physiological dependence liability
- Whether the substance is an immediate precursor of an already-scheduled substance

Two federal agencies, the DEA and the Food and Drug Administration (FDA), determine which substances are added to or removed from Schedules I-V.[12] The CSA assigns a regulatory role to the Department of Health and Human Services (HHS), which is delegated to the US Food and Drug Administration (FDA).[12] The FDA is responsible for scientific and medical assessments of drugs and for making scheduling recommendations to the DEA.[21]

Each schedule is defined as shown in Table 1. Schedule I drugs have the highest risk for SUD and misuse and no accepted medical uses. Cannabis, although legal in some states, is still a Schedule I drug at the federal level. It is the only Schedule I drug that is legal at the state level for medicinal and recreational uses. The DEA does allow research to be conducted with Schedule I drugs when an investigator is deemed to be qualified and the protocol is found to have merit.

Schedule II medications do have accepted medical uses (some with restrictions), including opioids for acute or chronic pain severe enough to warrant an opioid prescription and stimulants used to treat attention deficit hyperactivity disorder (ADHD). Use of Schedule II drugs may lead to severe psychological or physical dependence.

Table 1. Drug Schedules I-V Established by the Controlled Substances Act

Schedule	Risk Level	Medical Use Status	Prescriptions	Refills allowed	Examples
I	Highest risk for SUD and misuse	No currently accepted medical use Lack of accepted safety for medical use	No	N/A	Heroin LSD Mescaline MDMA Methaqualone Marijuana
II	High potential for SUD and misuse (less than Schedule I)	Currently accepted medical use	Paper Electronically transmitted with strict requirements Phone only in emergencies with written prescription to follow within 7 days	No*	Amphetamine Opioids: Codeine Fentanyl Hydrocodone Hydromorphone Meperidine Morphine Methadone Opium Oxycodone Methylphenidate Pentobarbital
III	Less potential for SUD and misuse than Schedules I or II	Currently accepted medical use	Paper Electronically transmitted Phone, fax	Up to 5 refills within 6 months	ACET with codeine Anabolic steroids Buprenorphine Ketamine
IV	Low potential for SUD and misuse relative to Schedule III**	Currently accepted medical use	Paper Electronically transmitted Phone, fax	Up to 5 refills within 6 months	Benzodiazepines: Alprazolam Clonazepam Diazepam Lorazepam Midazolam Temazepam Triazolam Carisoprodol
V	Low potential for SUD and misuse relative to Schedule IV	Currently accepted medical use	Paper Electronically transmitted Phone, fax	No limits, except partial refills must occur within 6 months of issue date	Cough preparations with codeine Ezogabine

SUD = Substance-use disorder
LSD = Lysergic acid diethylamide
MDMA = Methylenedioxymethamphetamine
ACET = Acetaminophen
*See exceptions under "Federal Restrictions Regarding Refills"
**Benzodiazepines carry risks of substance dependence and respiratory depression, particularly in combination with other substances that also depress respiration.[21,22]

The medications in Schedule III may lead to a moderate or low degree of physical dependence or "high." Schedule III opioids include products containing not more than 90 mgs of codeine per dosage unit. This is also the schedule that contains stimulants and anabolic steroids.

Although Schedule IV drugs are considered to have low potential for SUD and misuse relative to Schedule III, cautions do apply. This schedule contains medications that are frequently prescribed for insomnia and anxiety disorders. These drugs, which include alprazolam, diazepam, and lorazepam, are frequently mentioned in overdose statistics involving opioids, and expert guidance urges caution in their use and taper and particularly discourages the combination with opioids unless deemed absolutely necessary.[13,22,23]

Schedule V contains drugs with limited quantities of opioids that include cough preparations, containing no more than 200 milligrams of codeine per 100 milliliters or per 100 grams. Although this lower schedule has less misuse danger relative to other schedules, patients prescribed any CS still must be managed with care.

Part of the role of the DEA is to ensure medications are not diverted for misuse. Table 2 contains common terms associated with the use and misuse of opioids and other prescription drugs that are categorized under CS schedules.[5] The DEA provides manuals for HCPs and other practitioners to keep abreast of federal requirements in implementing the CSA.[24] As of this writing, the DEA Diversion Control Division is currently updating all manuals but did issue an updated pharmacist's manual as of 2020.

The Purpose of a Prescription in Legitimate Medical Practice

The DEA tracks the flow of CS from manufacture to ultimate use and enforces the CSA, including the tenets of lawful prescribing.[12] In order to be legal, a CS prescription must be issued for a legitimate medical purpose in the course of professional practice.[25] In general, this means HCPs must practice in accordance with medical standards recognized and accepted in the United States.[24] The totality of circumstances particular to each HCP and patient must be evaluated on its own merits.

Registration Requirements to Prescribe Controlled Substances

The cornerstone of CS regulation is that all handlers of CS must register with the DEA. The registration requirement extends to HCPs, drug manufacturers, wholesale distributors, hospitals, pharmacies, and scientific researchers.[26] One person or the institution itself (for example, a hospital) may serve as the registrant, and nonregistered agents may write prescriptions under that registration.[24] If an HCP has than one practice, each location must have its own DEA registration to prescribe CS.[24] This applies to a business location and not to HCPs who practice at multiple locations within the same state.

When it comes to DEA registration, HCPs should be vigilant regarding renewal dates and deadlines and also keep current with any requirements that may have changed.[27] Registration renewals take place every 3 years. New or renewal applications can be initiated here: DEAdiversion.usdoj.gov or by calling 1-800-882-9539.

The DEA may act to suspend or revoke a prescriber's registration, for example, if the prescriber has:[24]

- Falsified any application
- Been convicted of a felony related to a CS
- Had a state license or registration suspended, revoked, or denied
- Committed an act that would render DEA registration inconsistent with public interest
- Been excluded from participation in a Medicaid or Medicare program

Considerations in determining the public interest include recommendations of state licensing boards, compliance with CS law at the state, federal, or local level, conviction record pertaining to CS, experience with respect to CS, and "such other conduct" that may threaten public health and safety.[24] The registrant takes responsibility for compliance with the CSA and for ensuring CS are distributed only to those authorized to receive them.[24] A registrant must notify the local DEA Diversion Field Office in writing within a business day of discovery of a theft or significant loss of a CS.[21]

The DEA may also move to investigate a prescriber for alleged criminal acts. The agency assures HCPs that investigation and prosecution are reserved for instances where "conduct is not merely of questionable legality, but instead is a glaring example of illegal activity," and that cases "typically involve facts that demonstrate blatant criminal conduct;" however, the agency does not set a clear standard or signify a basis for prosecution.[26] The DEA does provide some examples of prescribing in violation of the CSA (i.e., for other than a legitimate medical purpose or outside the usual course of professional practice).[26]

Table 2. Definitions Related to Prescription Drug Use and Misuse

Term	Definition
Physical dependence	• Not the same as addiction • Occurs because of physiological adaptations to chronic exposure to a drug • Withdrawal symptoms occur when medicine is suddenly reduced or stopped or when antagonist is administered • Symptoms can be mild or severe and can usually be managed medically or avoided through slow drug taper
Tolerance	• Same dose of drug given repeatedly produces reduced biological response • Higher dose of drug is necessary to achieve initial level of response
Misuse	• Taking medication in a manner or dose other than prescribed • Taking someone else's prescription, even if for a medical complaint like pain • Taking medication to feel euphoria (i.e., to get high) • *Nonmedical* use of prescription drugs refers to misuse
Addiction	• Primary, chronic disease of brain reward, motivation, memory, and related circuitry • Dysfunction in circuits leads to characteristic biological, psychological, social, and spiritual manifestations as individual pathologically pursues reward and/or relief by substance use and other behaviors • Characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and dysfunctional emotional response • Involves cycles of relapse and remission • Without treatment or recovery activities, is progressive and results in disability or premature death
Opioid-use disorder	• A problematic pattern of opioid use leading to clinically significant impairment or distress • Defined in DSM-5* • Previously classified as "opioid abuse" or "opioid dependence" in DSM-4 • Also referred to as "opioid addiction"

*DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; diagnostic criteria given later in this activity

While there are no set criteria, some recurring patterns cited by the DEA that might indicate inappropriate prescribing include:[24]

An inordinately large quantity of CS or numbers of prescriptions in comparison to other area HCPs (while also recognizing that some practitioners, for example, those who treat cancer, may prescribe more than others)

- Lack of physical exam
- Warnings to the patient to fill prescriptions at different pharmacies
- Prescriptions issued that are known to be delivered to others
- Prescriptions issued in exchange for sex or money
- Prescribing intervals inconsistent with legitimate medical treatment
- Use of street slang for medical drugs
- No logical relationship between prescribed drugs and alleged medical condition

The DEA further clarifies that the existence of any of the foregoing factors does not automatically mean a prescriber has acted improperly. For example, some patients require doses that would be considered large for other patients, and the DEA asserts that each case is individually considered.[26]

Federal Record-Keeping and Security Requirements

The CSA has stringent record-keeping requirements. A complete and accurate inventory is required of all CS kept on the premises, which are subject to inspection. Complete records and inventories for Schedule I and II drugs must be kept separate from all other records.[24] Likewise, records for Schedules III-V drugs substances must be kept in a "readily retrievable" form or maintained separately from all other records.[21] Inventory requirements extend to samples received from pharmaceutical companies.

HCPs must maintain records any CS dispensed or prescribed and of certain direct administrations.[21] HCPs are not required to maintain copies of prescriptions except for opioids used in maintenance for addiction treatment or detoxification.[21] Certain states do require the use of multiple-copy prescriptions for Schedule II and some other CS.[21] Records related to CS must be kept available for inspection for at least 2 years.[24] The HCP should contact the local DEA field office to dispose of any CS that are no longer wanted (e.g., damaged, out-of-date) and keep records of the transfer and disposal.[24]

Controlled medications must be secured to guard against theft and diversion.[28] Factors affecting adequate controls include location of the premises, the type of building, the type and quantity of CS stored there, a storage safe, vault, or steel cabinet, the control of public access, the alarm and detection systems, and the availability of police protection.[24] The DEA is authorized to enter and inspect premises where CS are stored and dispensed.

Information on Prescriptions

CS prescriptions must be dated and signed on the day when issued and include the patient's full name and address as well as the registrant's full name, address, and registration number.[24] In addition, the prescription must include:[24]

- Drug name
- Drug strength
- Dosage form
- Quantity prescribed
- Directions for use
- Number of refills (may be 0)

CS prescriptions must be written in indelible ink or pencil or else be typewritten.[24]

Federal Restrictions Regarding Refills

Schedule II prescription orders must be written and signed by the HCP and may not be phoned into the pharmacy except in an emergency. If phoned in under emergency circumstances, the HCP must present the written and signed prescription to the pharmacy within 7 days.[21,24] One further exception is that a fax may serve as the written prescription for residents of long-term care facilities, hospice patients, or compounded IV opioids.[24]

The federal government does not set a time limit for when a Schedule II prescription must be filled, but some state do set limits.[24] Similarly, federal law does not limit the quantity of Schedule II CS; however, several states and insurance carriers do specify such limits, so it is important to know what regulations apply to one's practice.[24]

No refills are allowed for Schedule II drugs; a new prescription must be written.[24] However, an HCP may issue multiple prescriptions allowing up to a 90-day supply of a Schedule II CS with written instructions on subsequent prescriptions indicating the earliest date on which a pharmacy may fill each prescription. Known as "Do Not Fill Until," this practice is not intended to discourage HCPs from seeing their patients often,[24] but is allowed in recognition that some flexibility is sometimes necessary for patients who have mobility, transportation, or other issues in obtaining their necessary medication. To engage in this practice, the HCP must be fully compliant with the CSA and all state laws (some of which may prohibit the practice), and have concluded that the patient does not create an undue diversion or misuse risk.[24]

Prescriptions for Schedule III-IV drugs may be written or phoned in and may be refilled up to 5 times within 6 months of issue.[21] Schedule V drugs have no refill limits but are restricted in that the patient must be at least 18 years old and must offer some form of identification to fill a prescription.[21]

Electronic Prescribing

There is a clarification to the written prescription rules. A rule published in the Federal Register, effective as of June 1, 2010, gives HCPs the options of writing CS prescriptions electronically as long as software requirements are met and applicants to e-prescribe comply with the DEA authentication process as set forth in 21 C.F.R. §1311, found here: https://www.deadiversion.usdoj.gov/21cfr/cfr/1311/subpart_c100.htm.[21] The benefits of e-prescribing include reducing and streamlining clinic staff workload, preventing needless delays and adverse drug reactions, and allowing for seamless incorporation of prescriptions into the patient medical record. Medicare now mandates that all prescriptions for CS under Part D be transmitted electronically, and most states have begun to follow suit.

State Electronic-Prescribing Mandates

Laws to mandate electronic prescribing of CS are part of a national effort to combat the opioid epidemic. Most states have either implemented or plan to implement such mandates.[29] At the state level, mandates are tied to PDMPs and are aimed at identifying patients who engage in misuse or diversion and prescribers who facilitate misuse or diversion.

Some states have written penalties into law associated with the mandates. The federal mandate described under Medicare Part D law has no penalties written into law, although future enforcement is expected to begin in 2022. In general, penalty enforcement delays are mainly in recognition of the ongoing obstacles to adoption posed by interoperability issues between information technology products and systems. The American Medical Association (AMA) reports that while 70% of physicians prescribe electronically, only 20% are able to electronically prescribe CS.[30] This is principally because PDMPs and electronic health records are not well integrated under current technologies, although progress in this regard is being made. An interactive map with state legislation pertaining to electronic prescribing requirements for CS can be viewed here: https://www.rxnt.com/epcs-mandates/.

State Laws Governing Controlled Substances Prescribing

Each state has passed laws and regulations that govern many aspects of CS prescribing, and each HCP should check within the state of practice and take care to comply with all requirements. Furthermore, state directives are always changing. Common examples include:[31]

- Dose and treatment duration limits
- Expanded PDMPs and new requirements for their use
- Required continuing medical education
- Required written pain treatment agreements
- Required physical exam prior to prescribing
- Required bona fide patient-physician relationship
- Specified timing of follow-up visits and/or urine drug testing (UDT)
- Presentation of patient identification to a pharmacist
- Medicaid plans requiring single prescriber and single pharmacy for certain high-risk patients

The Prescription Drug Abuse Policy System (PDAPS), funded by the National Institute on Drug Abuse (NIDA), tracks key state laws related to prescription drug abuse here: http://www.pdaps.org/. All HCPs who prescribe CS are charged with compliance in regard to federal and state regulations as well as any local laws or polices. Whenever relevant state and federal CS regulations conflict, the more restrictive regulation applies.

Many states have requirements for checking the PDMP when prescribing scheduled CS, particularly opioids. Expectations may include checking before initiating or continuing prescriptions as well as the terms of periodic follow-up. The benefits of PDMPs in terms of safeguarding the integrity of treatment and increasing patient safety are many, including to:

- Verify real-time and past prescription histories, including the medication type, dosage, quantity, date dispensed, patient, prescriber, and pharmacy
- Alert to dangerous drug-drug interactions
- Alert to unauthorized CS prescriptions or unauthorized multiple providers/pharmacies
- Provide reports to licensing boards or law enforcement agencies
- Possess some capacities for data sharing across states and agencies, allowing integration into the electronic health record

Regular checks of the state PDMP can help HCPs detect unauthorized prescriptions, but because use and sharing of data across all states is not yet universal or compulsory, people who wish to obtain prescriptions to misuse or divert are still able to find places to do so, sometimes by traveling great distances.[32] Improving patient care will require improvements to health information technology and robust data sharing among organizations and providers across the states.[33] Meantime, progress is being made in that the AMA reports that more physicians are querying PDMPs than ever before with over 460 million queries in 2018, which is triple the 136 million queries in 2016.[30]

State medical boards regulate the practice of medicine and are responsible for ensuring that HCPs meet professional and ethical standards of care.[34] These boards oversee the licensing of HCPs, investigate complaints, and strive to protect the public. Discipline of a provider may include probation, restrictions to a license to practice, suspension of a license, or revocation of a license. However, an educational remedy may be deemed sufficient to resolve the problem.

In regard to professional practice standards related to CS prescribing, several states have adopted all or part of the Federation of State Medical Boards (FSMB): Guidelines for Chronic Use of Opioid Analgesics. This document was updated in April 2017 and aims to set reasonable guidelines for the prescription of opioid analgesics in the treatment of chronic pain.[35]

Guidelines vs. the Force of Law[36]

Numerous bodies hold sway in how CS are lawfully and appropriately prescribed. Statutes and acts passed by legislative bodies are laws. Regulations are rules written by government agencies to explain the law and are enforced as law. In addition, numerous opioid-prescribing practice guidelines have been published by professional associations, government agencies, and other bodies to assist HCPs.[13,35,37-39] These types of policy statements, guidelines, and position statements are not laws but are sometimes introduced as evidence in court or otherwise come to be seen as the standard of the care.[5]

In 2016, Centers for Disease Control and Prevention (CDC) issued a practice guideline for using opioids to treat patients who have chronic pain and do not have an active malignancy or need palliative or end-of-life care.[13] However, the CDC guideline has had certain misapplications and unintended consequences and has sometimes been enforced inflexibly with regard to treatment duration, dosage limits, and the recommendation to taper opioids.[40] Authors of the guideline state that its strictures should not be used to deny clinically-appropriate opioid therapy to patients but, rather, to help HCPs in primary care consider all treatment options with an eye to reducing inappropriate opioid use.[41]

Commonly Prescribed Controlled Substances

The 5 drug classes regulated by the CSA are opioids (called "narcotics" by the DEA), sedative-hypnotics, stimulants, hallucinogens, and anabolic steroids. Each class produces its own effects in the body, but all share the commonality that they have the potential for being misused by patients and non-patients. They are also among the most highly sought-after drugs for diversion.[42] With the exception of anabolic steroids, CS are sought by people who seek to alter mood, thought, and feeling through the drug's central nervous system (CNS) action. Motivations are many and may include to experience euphoria or increased energy, to alleviate pain, anxiety, depression, or insomnia, to avoid withdrawal symptoms, or because an addictive disorder has developed.

Many CS drugs are commonly prescribed for indicated medical conditions. Others, such as cocaine, have very limited medical indications. Non-opioid medications can minimize opioid exposure, and different medications can complement one another; however, each has unique risks and benefits as well as mechanisms of action,[5] and their effects can be synergistic when used in combination.[5] A risk-benefit analysis is always recommended based on the individual patient's medical, clinical, and biopsychosocial circumstances.[5]

Each category will be further described in the sections that follow. HCPs should bear in mind that in medical treatment, there is a preferential role for nonpharmacologic treatments and non-CS medications.[5,13] These can be used alone or in combination with CS medications, when indicated.

Anabolic Steroids

Anabolic steroids, also called anabolic-androgenic steroids, are performance-enhancing drugs that are synthetically manufactured derivatives of the male hormone, testosterone.[43] Anabolic steroids bind to and saturate certain androgen receptors, upregulating and increasing the number of receptors[43,44] Their action in the body activates protein synthesis and decreases protein breakdown as a means to decrease fat mass and increase muscle mass.[43] Examples include methandienone, methyltestosterone, oxandrolone, and stanozolol.[45]

Positive and negative effects in body involve multiple organs and systems (e.g., reproductive tissues, muscle, bone, liver, kidneys, and CNS).[43,45] The physical and psychological effects can be short- and long-term and are particularly concerning due to potential toxicity in the cardiovascular and reproductive system. Some potential effects are:[43,46,47,43,47,48]

- Hypogonadism
- Neurodegeneration
- Cardiac impairment
- Coronary artery disease
- Sudden cardiac death
- Aggression
- Depression

Damage to the body occurs by such mechanisms as oxidative stress, apoptosis, and protein synthesis alteration.[43] Physiologic effects result from amplifying testosterone and estrogens. Clinical and experimental studies have shown that increased activity of the renin-angiotensin-aldosterone system plays a pivotal role in the pathogenesis of cardiological diseases.[43]

Prescription testosterone products are FDA-approved as hormone replacement therapy for men who have low testosterone due to failure of the testicles to produce testosterone because of genetic problems or damage.[44,49] Primary hypogonadism causes include delayed puberty in boys, hypogonadotropic hypogonadism, gonadotropin and luteinizing hormone-releasing hormone deficiency, and pituitary-hypothalamic axis dysfunction from various tumors, injury, and radiation.

Other medical uses and indications include breast cancer, low red blood cell count, chronic kidney disease, osteoporosis, bone marrow stimulation in leukemia, aplastic anemia, kidney failure, growth failure, stimulation of appetite, and treatment of muscle mass in malignancy and acquired immunodeficiency syndrome.[43,44,50,51] Anabolic steroids can reverse cachexia in several disorders (e.g., HIV, liver disease, renal failure, some malignancies, burn patients) but vigilance is necessary to reduce their misuse and potential for diversion.[44] Even though the most common source of illegal steroids is smuggling from illegal markets, HCPs should be mindful that thefts or inappropriate prescribing can also send steroids into the illicit market, making responsible prescribing and monitoring important.[51]

Many common uses are not FDA-approved, including to improve increase strength and physical performance.[51] Lifetime prevalence of use is 1% to 5% worldwide,[47] primarily in male athletes and other males.

People who should not use exogenous testosterone include those with renal, cardiac, and hepatic disease, venous thromboembolism, pregnant women (or women who may become pregnant), breastfeeding women, and men with breast cancer or prostate cancer.[44] The Endocrinology Society suggests avoiding treatment with testosterone in men who have a history of myocardial infarction and stroke in the previous 6 months.[44]

Routes of administration are oral, injection, creams, pellet implantation, or transdermal patches.[51] The length of time that steroids or their metabolites stay in the body varies from a couple of days to more than 12 months.[51]

To initiate treatment, a diagnosis of hypogonadism should be confirmed by measuring early morning testosterone levels on 2 separate days.[44] Patients older than 40 years should receive a prostate exam and the following lab tests: lipid profile, hepatic function, hemoglobin, hematocrit, and prostate-specific antigen (PSA).[44] The lipid profile and hepatic function tests, hemoglobin, and hemocrit should be checked at 3-6 months, then annually thereafter.[44] Monitoring for response should follow the same schedule and focus on cardiac adverse events and signs of virilization in women treated for breast cancer.[44] Men with a palpable prostate nodule or PSA more than 4 ng/mL and patients at high risk of prostate malignancy with PSA more than 3 ng/mL should not receive testosterone treatment.[44]

Treatment recommendations are as follows:

- With injections, measure testosterone level midway between injections of testosterone enanthate and testosterone cypionate, adjusting dose and frequency to keep testosterone concentration between 400 ng/dL and 700 ng/dL[44]
- With topical solutions, measure testosterone 2-8 hours after application and after 14 days of starting therapy or with dose titration[44]
- With nasal testosterone gel, measure total serum testosterone periodically starting the first month after initiation of therapy and terminate treatment if it exceeds 1050 ng/dL
- With transdermal testosterone, measure serum testosterone level approximately 14 days after starting therapy in the morning before application[44]
- With testosterone pellets, measure serum testosterone level at the end of the dosing interval[44]
- With a buccal formulation, measure serum testosterone level 4-12 weeks after initiation of treatment and before the morning dose[44]

Anabolic steroids are sought-after for misuse and may result in SUD. Misuse at higher doses than commonly prescribed for medical purposes can have serious consequences.[49,51] In 2016, the FDA issued updated class-wide safety information for all prescription testosterone products and added a warning regarding risk of misuse and dependence.[49] Although illegal and prohibited by sports organization, athletes misuse stimulants, both prescription drugs with approved medical indications and illicit "designer" drugs with no medical value. Other frequent misuse occurs by school children, teens, and young people, including males and females.[44] Misuse by law enforcement personnel is documented as well.

All HCPs who prescribe testosterone products should be aware of the misuse potential and serious adverse outcomes, especially those related to cardiovascular and mental health.[49]

HCPs should also be cognizant that misuse often involves use of several steroid products at doses higher than usually indicated for medical use. Reported serious outcomes of misuse have included:[49]

- Heart attack
- Heart failure
- Stroke
- Depression
- Hostility
- Aggression
- Liver toxicity
- Male infertility
- Withdrawal symptoms at high doses (e.g., depression, fatigue, irritability, loss of appetite, decreased libido, insomnia)

Research indicates that people who take anabolic steroids for performance- and body-enhancing purposes frequently do not disclose their use to their doctors and do not trust medical professionals to give them accurate, nonjudgmental information.[43] Therefore, needed blood tests and other safety monitoring often does not occur. In people who are not competing at elite levels but are using anabolic steroids to enhance performance, the best manner of detecting use may be to ask using nonjudgmental language.[47]

Testing can reveal the following causes for concern:

- A heightened level of aldosterone is considered to be related to the occurrence of cardiac illnesses, even in the absence of hypertension.[43]
- Anabolic steroid metabolites in urine may be a predictive factor of cardiac changes.
- Results that suggest anabolic steroid use include very low serum high-density cholesterol and sex hormone-binding globulin concentrations and unexplained erythrocytosis.[47]

Appropriate education could be crucial to alerting athletes and others with performance-enhancement goals to the potential harms and that sophisticated blood and urine screens have been devised to detect these drugs.[44] In addition, some substances obtained online may be counterfeit and contain additives that may be toxic.[44] In addition to risk of addiction, users should be helped to understand that psychoactive effects of anabolic steroids could be deadly as a result of associated anger, suicidal thoughts, rage, and extreme violence.[44] Referral for mental-health specialty care or other specialists as indicated could be life-saving.

Withdrawal from anabolic steroids might precipitate and anxiety and depression,[47] which can be managed with behavioral and medication therapy. Men who have used anabolic steroids for less than year typically recover normal hypothalamic-pituitary-testicular axis function within a year after stopping.[47] Additional therapies common in fertility treatment may be considered on a short-term basis for those with longer-term, high-dose use.[47] Patients should be counseled to the risks and perhaps provided with reading sources. A number of resources are available to educate patients, many also available in Spanish. These include:

- "Performance-Enhancing Drugs: Know the Risks." Mayo Foundation: https://www.mayoclinic.org/healthy-lifestyle/fitness/in-depth/performance-enhancing-drugs/art-20046134
- "Are Steroids Worth the Risk?" For Teens (also in Spanish). Nemours Foundation: https://kidshealth.org/en/teens/steroids.html
- "Teens and Steroids: A Dangerous Combo." FDA: https://www.fda.gov/consumers/consumer-updates/teens-and-steroids-dangerous-combo
- "Anabolic Steroids Drug Facts." NIDA: https://www.drugabuse.gov/publications/drugfacts/anabolic-steroids

BEFORE MOVING ONTO THE NEXT SECTION, PLEASE COMPLETE CASE STUDY 1 ON THE NEXT PAGE.

Depressants and Sedative-Hypnotics

The class of depressants includes many widely misused medications. Furthermore, from 2004 to 2019, benzodiazepines and sleep medications zolpidem, zaleplon, and zopiclone were (together with opioids) the most commonly dispensed categories of CS in the United States (Figure 2).[4] Benzodiazepines (Schedule IV) are prescribed for short-term use as anxiolytics and for insomnia. Benzodiazepines include:[52]

- alprazolam
- chlordiazepoxide
- clonazepam
- clorazepate
- diazepam
- estazolam
- flurazepam
- lorazepam
- midazolam
- oxazepam
- temazepam
- triazolam
- quazepam

Case Study 1

Instructions: Spend 5–10 minutes reviewing the case below and considering the questions that follow.

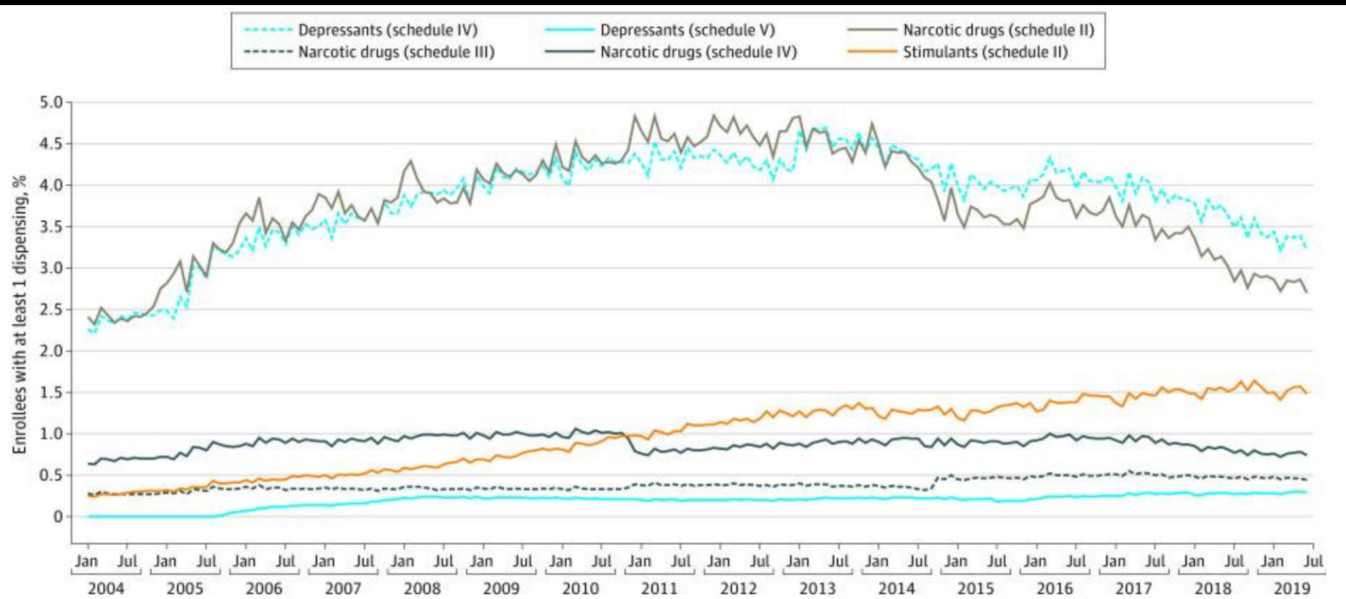
Brandon, a 17-year-old high school wrestler, has been brought to his primary care physician by his mother after he exhibited a personality change that included fits of violent rage, one in which he broke furniture in his bedroom. He has been evaluated for bipolar, ADHD, depression, and anxiety with negative results. He denies use of caffeine, alcohol, nicotine products, or marijuana. He admits that he is worried about weight gain from overeating and sought a method to build muscle instead of fat while continuing to eat his usual diet, which is heavy in processed foods and sugar. He purchased steroids from an Internet site and has been taking them for several months, but he is unable to say what type or dosage he is on.

1. **What laboratory tests might be indicated?** _____

2. **What counseling regarding steroid consumption is indicated?** _____

3. **What type of referral(s) might be given?** _____

Figure 2. Trends for Most Commonly Dispensed Categories of Controlled Substances in US Commercially-Insured Adults (January 2004 to June 2019)*



Six most commonly dispensed categories as of January 2019-June 2019 are presented:
Depressants (schedule IV) contained benzodiazepines and sleep medications zaleplon, zolpidem, and zopiclone
Depressants (Schedule V) contained brivaracetam, ezogabine, lacosamide, and pregabalin
Opioids (Schedule III) contained codeine ≤90 mg per dosage, morphine ≤50 mg/100 mL or 100 g, both in a combination with another non-opioid ingredient, and buprenorphine
Stimulants (Schedule II) contained amphetamine, methamphetamine, methylphenidate, lisdexamfetamine, and dextroamphetamine
*Based on de-identified longitudinal claims data on beneficiaries of a large US employer-sponsored commercial health insurance provider and covers approximately 9 million individuals ages 19 to 64 years in any given month across all 50 states.

Benzodiazepines appear to affect neurotransmitters in the brain, in particular, enhancing gamma-aminobutyric acid GABA with the effect of reducing anxiety.[52] Onset and duration of action vary among benzodiazpines.[52] For example, lorazepam has a rapid onset and a half-life of 12 hours, oxazepam has a slow onset and a half-life of 8 hours, and temazepam has a half-life of 10 hours. Long-acting benzodiazepines include chlordiazepoxide and diazepam. Lorazepam, alprazolam and clonazepam are intermediate onset. Clorazepate, midazolam, and triazolam, are short-acting agents with durations of action of 3 to 8 hours.

Prescriptions for benzodiazepines have increased along with involvement in overdose deaths.[53] An FDA boxed warning details the risks of prescribing opioids and benzodiazepines together, a combination of medications that has increased in recent years but which is associated with extreme sleepiness, respiratory depression, coma, and death.[22,37] The CDC recommends against combining these 2 medications whenever possible but allows for rare instances when the combination may be indicated (e.g., severe acute pain in the presence of long-term, stable, low-dose benzodiazepine therapy).[13] The Department of Veterans Affairs/ Department of Defense (VA/DoD) practice guideline lists concomitant use of benzodiazepines as a contraindication to initiating a trial of long-term opioid therapy.[37]

Benzodiazepines should be stopped gradually and perhaps with the help of a specialist. Abrupt cessation with not only benzodiazepines but also baclofen, carisoprodol, or barbiturates, can cause significant morbidity and even death.[54] Acute withdrawal symptoms with sedative-hypnotics can include anxiety, tremors, tachycardia, fever, hypertension, insomnia, seizure, and delirium.[54-56]

Scheduled sleep medications include zaleplon, zolpidem, and zopiclone (Schedule IV), known as "Z-drugs," and brivaracetam, ezogabine, and lacosamide (Schedule V). Like benzodiazepines, Z-drugs enhance the effect of GABA, the major inhibitory neurotransmitter. Evidence shows they have reinforcing effects and carry risks for abuse potential, tolerance, physical dependence, and subjective effects.[57] While Z-drug addiction is uncommon, the risk increases at higher doses and in patients with an SUD history.[57] Z-drugs can cause withdrawal symptoms if abruptly discontinued after prolonged use. Side effects include nightmares, agitation, hallucinations, dizziness, daytime drowsiness, headache and gastrointestinal (GI) problems.

Barbiturates include amobarbital, pentobarbital, phenobarbital, secobarbital, and tuinal. Some are very short-acting drugs with effects lasting only a few minutes while others may have effects that last up to 2 days.[58] Barbiturates have a history of medical uses as sedative-hypnotics for insomnia and anxiety but also have a history of recreational misuse and a narrow therapeutic index.[59] Current medical indications largely center on preoperative sedation and antiseizure, and misuse has dropped in recent decades as barbiturates have been largely replaced in practice by benzodiazepines.[59] With misuse at low doses, people feel drowsy, disinhibited, and intoxicated; at higher doses, they begin to stagger and develop slurred speech and confusion, possibly resulting in coma and respiratory depression leading to death.[58] Withdrawal symptoms include difficulty sleeping, agitation, tremor, hallucinations, high temperature, and seizures.

Gabapentinoids: Uses and Precautions

Gabapentinoids are effective in the treatment of neuropathic pain,[60] which is caused by damage to or abnormal processing of the CNS or peripheral nervous system and is often refractory to treatment.[61] Benefits are that gabapentinoids can be considered opioid-sparing and even reduce benzodiazepine use.[62] These benefits led the CDC to recommend gabapentinoids as first-line agents for neuropathic pain.[13] Their use in clinical practice is increasing: gabapentin was the 10th most commonly prescribed medication in the United States in 2016 with 64 million prescriptions dispensed, up from 39 million in 2012.[63]

However, reports of misuse and mentions in overdose events are also rising.[10,62,64,65] The prevalence of misuse and diversion of gabapentinoids as well as the motivations, risk factors, and frequent combination with opioids must be understood and appreciated by HCPs in order to increase patient safety and optimize chances for good treatment outcomes.[64,66]

Two gabapentinoids, developed as anticonvulsants, that are also commonly used in clinical pain treatment plans are pregabalin and gabapentin. Pregabalin is a Schedule V drug with FDA-approved indications for post-herpetic neuralgia (PHN) and as an adjunct therapy for partial seizures, fibromyalgia, renal impairment, neuropathic pain from diabetic peripheral neuropathy, and spinal cord injury.[67] Gabapentin is currently not scheduled in most states but has been recently reclassified as a Schedule V drug in Kentucky, Michigan, and Tennessee, and is facing new regulatory requirements in other states.[11,68] Gabapentin's FDA-approved indications are for PHN and as an adjunct therapy for partial seizures.[11,69] In addition to having mild-to-moderate benefit for neuropathic pain syndromes, gabapentinoids are also commonly used to treat migraine and as part of a multimodal approach to treating perioperative pain.[5]

Gabapentinoids do not act on GABA receptors but on the alpha-2-delta-1 subunit of calcium channels in the CNS, ultimately reducing release of excitatory neurotransmitters.[33] The action blocks nerve pain and seizures but, at therapeutic doses, some people also experience relaxation and euphoria.[33] Pregabalin has approximately 6 times higher binding affinity for the alpha-2-delta-1 subunit than gabapentin. There are also differences in absorption between the 2 medications. Pregabalin's absorption increases proportionally with dose, and the bioavailability of pregabalin is 90% regardless of the dose.[33] In contrast, gabapentin is saturable in terms of absorption with the bioavailability being 60% for a 300-mg dose and 35% for a 1600-mg dose.[33]

There is limited research on off-label uses of gabapentinoids, although such use does occur. They are frequently prescribed for restless leg syndrome and diabetic neuropathy, and gabapentin has been used to treat alcohol-use disorder, although such use should be weighed against the risk for misuse.[33] One systematic review and meta-analysis of randomized controlled trials of treatment with pregabalin or gabapentin for chronic low-back pain found little-to-no benefit compared with placebo or other analgesics.[70] Adverse effects reported more commonly with gabapentin than placebo included dizziness, fatigue, difficulties with mentation, and visual disturbances. The investigators said more evidence is needed but called for caution in using gabapentinoids for chronic low-back pain, given the lack of efficacy, risks, and associated costs.

Common adverse effects include sedation, drowsiness, cognitive slowing, dizziness, ataxia, and a risk of misuse.[10] Because they may cause euphoria, dissociation, relaxation, sedation, and sometimes psychedelic effects, gabapentinoids do have abuse potential. The risk of misuse is more common in people with prior misuse of opioids.[10] This relationship is important because of the common practice of co-prescribing gabapentinoids with other CNS-depressants used for pain control, including opioids, sleep aids, and antidepressants. When misused, gabapentinoids are sometimes taken in supratherapeutic doses and combined with other drugs to increase effects.[33] Gabapentin is easy to obtain for this purpose because it is not a CS in most states and is not a required substance in PDMP checks.[33]

Several indicators point to the need for clinical vigilance with gabapentinoids to ensure safe use by patients. Gabapentin misuse, toxicity, use in suicide attempts,[11] and associated healthcare utilization in United States increased significantly from 2013 to 2017.[1] Although gabapentin is less likely to result in fatal overdose than opioids, poison exposures did increase by 72.3% from 2013 to 2017.[1] Of the approximately 16% of overdose patients, about 60% had co-ingested benzodiazepines or opioids. and evidence suggests that co-prescription of opioids and gabapentinoids also may increase overdose risk.[37]

Some effort has been made to characterize the overdose risk factors so as to minimize the potential harm. In Scotland, investigators studied the rising mentions of gabapentinoids in drug-related deaths.[60] They found that, as elsewhere, more prescriptions were being written and that recurrent users were more likely to be older people, women, living in deprived areas, and that 60% were co-prescribed an opioid, benzodiazepine, or both. Yet they also found that most decedents (77%) in at least one area of the country had not received a prescription, suggesting that those deaths were more related to illegal use than prescribed medication.

Safe and effective use of gabapentinoids depends on targeting prescribing to the patient's medical condition, using care with co-prescriptions, and also knowing risk factors for poor outcomes.[71] Patients with a prior history of SUD are at risk for mismanaging gabapentinoids and engaging in unhealthy use patterns. HCPs should understand that the misuse risk is higher in combination with opioids, that gabapentinoids are often sought to heighten or attenuate the effects of other misused drugs, and that the overdose risk is greatest in combination with other prescribed drugs or illicit substances. A prudent course of action would be to consider including gabapentinoids in UDTs, when prescribed long term, to check that the medication is being taken as intended.[33] A consideration is that cost could be higher to include gabapentinoids as these medications are not part of a typical UDT check.

Patients taking gabapentinoids should be monitored for:[33]

- Changes in mood
- Frequent requests for early refills
- Requests for rapid increases in doses
- Unexpected results in UDTs

Cumulatively, these trends and findings suggest that gabapentinoids may be an effective first-line option for the difficult-to-control indication of neuropathic pain, but that vigilant clinical precautions and protocols should accompany their prescription to prevent misuse and diversion. Gabapentinoids may also offer a means of sparing opioid doses for refractory pain or in the perioperative setting. It is important to understand that co-prescribing gabapentinoids with another CNS-depressant, which is commonly done, adds risk with these medications.[60] HCPs should consider monitoring gabapentinoids via PDMP and UDT measures whenever possible.

Hallucinogens: Limited Medical Uses

Hallucinogens are synthetically made or plant-based and are marked by sensory and psychic effects that include perceptual distortions.[72] Physiological effects of the class can include elevated heart rate, increased blood pressure, dilated pupils, nausea, and vomiting. Medical research into the use of Schedule I hallucinogens has been increasing. Most are drugs that are used recreationally (e.g., hallucinogenic mushrooms, LSD, and MDMA or "ecstasy").

Few have medical indications with a notable exception being ketamine, a Schedule III drug with accepted medical uses for short-term sedation and anesthesia.[73] Ketamine is a dissociative anesthetic, distorting sight and sound and giving the patient a sense of detachment from pain and the environment. For this reason, it has been researched as a treatment for some types of intractable pain. In addition, the FDA has approved a nasal spray version of the S(+) enantiomer of ketamine (esketamine) for treatment-resistant depression that is only available at a certified doctor's office or clinic.[73] Ketamine misuse may lead to moderate or low physical dependence or high psychological dependence. Overdose can occur with ketamine and when serious can lead to respiratory depression, coma, convulsions, seizures, and death due to respiratory arrest.[73]

Opioids (Called "Narcotics" by DEA)

As Schedule II medications, opioid prescriptions are not limited by quantity or treatment by the CSA; however, many states and insurance carriers do set limits on quantity, frequency, and duration of prescriptions as well as other facets of treatment and monitoring. Remember that the more restrictive law trumps the less restrictive in regard to prescribing CS. Prescribing for pain has dropped off in recent years after peaking in 2011.[18] However, the danger from the opioid crisis is ongoing, and HCPs are called on to prescribe judiciously, reserving opioids for pain that does not respond to other treatments.

Opioids are used to treat acute pain from injury or surgery and chronic pain that goes beyond the time of normal healing or from a long-term condition or disease. Pain often results from neurologic and musculoskeletal conditions as well as local or systemic complications of diseases. For some patients, acute pain may become chronic. Chronic pain syndromes have associations with many long-term conditions and diseases. Biological, psychological, and social factors all contribute to the experience of pain, a concept known as the biopsychosocial model.[5]

Opioids are classified according to their action at mu receptors as full agonists, mixed agonist-antagonists, or antagonists (Table 3).[74-77]

Table 3. Opioid Analgesic Classifications

Type	Generic Name	Notes/Cautions
Pure agonists	Codeine Dihydrocodeine Fentanyl Hydrocodone Hydromorphone Levorphanol Meperidine* Methadone Morphine Oxycodone Oxymorphone Propoxyphene	*Meperidine not recommended for long-term treatment or in patients with renal compromise due to toxicity risks
Agonist-antagonists	Partial agonist: Buprenorphine Mixed agonist-antagonists: Butorphanol Dezocine Nalbuphine Pentazocine	May produce withdrawal with physical dependence
Pure antagonists	Naloxone Naltrexone	Administered to reverse opioid effects
Other	Tramadol Tapentadol	Dual action mu-agonist and serotonin–norepinephrine reuptake inhibitor Dual action mu-agonist and norepinephrine reuptake inhibitor

Most clinically-prescribed opioids are full mu agonists. Buprenorphine has a reduced potential for respiratory depression and acts as an antagonist at the kappa receptor, which is shown to reduce anxiety, depression, and the unpleasantness of opioid withdrawal.[5] Tapentadol and tramadol have dual modes of action as agonists at the mu receptor and SNRIs.[5] Considerations with dual-mechanism opioids include lowering of the seizure threshold in susceptible patients and the risk of serotonin syndrome.[37]

Formulations may be extended-release (ER) or immediate-release (IR), and delivery systems for outpatients include oral, transmucosal, and transdermal routes of administration. Combination products contain products such as acetaminophen (ACET) together with an opioid, necessitating careful tracking of daily dose limits so as not to incur risk for liver and GI toxic effects.[78] All transdermal and transmucosal fentanyl and hydromorphone ER products are for use only in opioid-tolerant patients and never for acute or short-term pain.[79] ER/LA opioids are primarily intended to be taken once or twice a day, are not indicated for acute pain, and are for use only in patients who are already tolerant to opioids.[13,79]

The primary risk with opioids is respiratory depression leading to death. Some opioids (e.g., methadone) can prolong the QTc interval. ER/LA opioid tablets should be swallowed whole, never crushed, chewed, broken, cut, or dissolved, which may result in rapid release and absorption of a potentially fatal dose.[79,80] Transdermal systems and buccal films should not be cut, torn, or damaged before use nor chewed, swallowed, or patches exposed to heat, which may lead to fatal overdose.

Possible opioid side effects include but are not limited to:[5,13]

- Lightheadedness
- Dizziness
- Sedation
- Nausea and vomiting
- Drowsiness
- Mental clouding
- Constipation
- Hormonal deficiencies
- Pruritis
- Myoclonus
- Irritability
- Respiratory depression

Certain cautions are necessary for special populations. Women should be informed of the risks of long-term opioid therapy during pregnancy to the developing fetus, including neonatal opioid withdrawal syndrome (NOWS),[13,81] birth defects, preterm delivery, poor fetal growth, and stillbirth.[13] Adults older than 65 years need cautious opioid dosing and consideration of risks that include falls, cognitive effects, interaction with other medications, and increased sensitivity to analgesic effects.[38] Initial doses should be 25–50% lower than in those who are younger.[82] Caution is necessary when initiating and titrating opioid doses in people with renal and hepatic impairment.[83]

Signs of an opioid overdose include:[84,85]

- Small, constricted "pinpoint pupils"
- Falling asleep or loss of consciousness
- Slow, shallow breathing
- Choking or gurgling sounds
- Limp body
- Pale, blue, or cold skin
- Snoring heavily and cannot be awakened
- Periods of ataxic (irregular) or other sleep-disordered breathing
- Trouble breathing
- Dizziness, confusion or heart palpitations

Stimulants

Schedule II stimulants include amphetamine, methamphetamine, methylphenidate, lisdexamfetamine, and dextroamphetamine.[4] Prescriptions have increased significantly,[4] and involvement in overdose deaths is increasing. During 2015–2016, age-adjusted psychostimulant-involved overdose death rates increased by 33.3% as part of what has been called a "growing polysubstance landscape."[86] From 2016 to 2017, death rates involving cocaine and psychostimulants increased across age groups, racial/ethnic groups, county urbanization levels, and multiple states.[86] Among all 2017 drug overdose deaths, 10,333 (14.7%) involved psychostimulants that include prescription drugs, such as dextroamphetamine and methylphenidate.[86]

Opioids frequently contribute to stimulant-involved overdose deaths.[86] However, stimulant deaths are also increasing without opioid involvement. Death rates involving cocaine and psychostimulants, with and without opioids, have increased, and synthetic opioids frequently are involved.[86] Responses should evolve to improve access to care, focus on protective and risk factors for substance use, and improve risk reduction messaging.[86] Harm reduction might also include expanded surveillance measures and naloxone availability.

Effects of stimulants as a class include increased alertness, wakefulness, and concentration.[87] Common medical indications include ADHD, obesity, and narcolepsy. Stimulants are associated with adverse effects such as tolerance, risks with withdrawal, and potential for misuse and SUD.[87] With abrupt cessation, withdrawal can be marked by depression, anxiety, and extreme fatigue.[87] Signs of a stimulant overdose include high fever and convulsions, and cardiovascular collapse may precede death.[87] Physical exertion can increase these hazards.

Carisoprodol

Carisoprodol is the only muscle relaxant that is a scheduled drug (Schedule IV).[88] It metabolizes meprobamate with hypnotic, anti-anxiety, sedative, anticonvulsant, and some indirect muscle relaxant properties that can cause drowsiness and dizziness. This medication is not recommended for long-term use or by those with a history of addiction. Because of its limited clinical effectiveness and elevated risks, general use of this medication is best avoided.

Prescribing for Common Conditions

Anxiety

Anxiety is a basic human emotion that can help the person adapt to danger and whose symptoms range from mild to severe.[89] With the understanding that fear and anxiety can be non-pathologic and transient emotions, HCPs should recognize that pathologic anxiety disorders persist longer than 6 months, are no longer developmentally appropriate, and are out of proportion to the threatening event or object.[90] These symptoms must cause distress, significantly alter the patient's routine, and diminish his or her functioning.[89] Symptoms must also not be better explained by another medical disorder or the physiological effects of a substance such as a medication or drug abuse. Anxiety disorders are highly prevalent in society, affecting millions worldwide, and are closely associated with stress.[91]

Examples of anxiety disorders include separation anxiety disorder, specific phobias, social anxiety disorder, panic disorder, agoraphobia, and generalized anxiety disorder (GAD). Anxiety disorders are described and classified in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), [92] and obsessive compulsive and trauma-related disorders are also common causes of anxiety symptoms, though the DSM-5 has separated them from other anxiety disorders.[90] Anxiety disorders often co-occur with each other and also with major depressive disorder.[93] Drug misuse can be another cause of anxiety disorder.[91] The disorders for which most people seek help in clinical settings are GAD, panic disorder, and social anxiety disorder.[93]

Rating scales to screen for severity and monitor treatment progress include the following:

- Hamilton Anxiety Scale for GAD[94]
- Panic and Agoraphobia Scale for panic disorder and agoraphobia[95]
- Liebowitz Social Anxiety Scale for social anxiety disorder[96]

HCPs can find disorder-specific rating scales in the electronic version of the DSM-5 to characterize the severity of each disorder and to track changes over time.[90] The scales are developed to have the same format but a different focus across the various anxiety disorders and to rate the physical, behavioral and cognitive ideation symptoms relevant to each disorder.[90] See Table 4 for the DSM-5 criteria for GAD.[97] The specificity of diagnostic criteria for each disorder is aimed at increasing treatment precision.[97]

In order to plan treatment and track the patient's response, it is important to specify what severity level of anxious distress is present.[97] Panic disorder can be seen with any DSM-5 disorder and is known to affect treatment response.[97] High levels of anxiety have been associated with higher suicide risk, longer duration of illness, and greater likelihood of treatment nonresponse.[97]

Table 4. Criteria for Generalized Anxiety Disorder from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition	
A.	Excessive anxiety and worry more days than not for at least 6 months about a number of events or activities, such as work or school performance
B.	Difficult to control worry
C.	Anxiety and worry associated with 3 or more (1 item for children) of the following 6 symptoms, at least some symptoms having been present for more days than not for the past 6 months: • Restlessness, feeling keyed up or on edge • Being easily fatigued • Difficulty concentrating or mind going blank • Irritability • Muscle tension • Sleep disturbance: difficulty falling or staying asleep, or restless, unsatisfying sleep
D.	Anxiety, worry, or physical symptoms cause clinically-significant distress or impairment in social, occupational, or other important areas of functioning
E.	Disturbance not attributable to physiological effects of a substance (e.g., drug of abuse, medication) or another medical condition (e.g., hyperthyroidism)
F.	Disturbance not better explained by another medical disorder (e.g., anxiety or worry about having panic attacks in panic disorder, negative evaluation in social anxiety disorder [social phobia], contamination or other obsessions in obsessive-compulsive disorder, separation from attachment figures in separation anxiety disorder, reminders of traumatic events in posttraumatic stress disorder, gaining weight in anorexia nervosa, physical complaints in somatic symptom disorder, perceived appearance flaws in body dysmorphic disorder, having a serious illness in illness anxiety disorder, or content of delusional beliefs in schizophrenia or delusional disorder)

Physical symptoms associated with anxiety include chest tightness, dyspnea, tachycardia, flushing, dry mouth, tremor, dizziness, blurry vision, nausea or vomiting, abdominal pain, diarrhea, and urinary urgency.[98]

Although drug development is ongoing to seek new targets for treatment, little progress has been made toward introducing new pharmacologic therapies, and many anxiolytics are CS with serious risks for SUD and drug interactions.[91] These include benzodiazepines (e.g., alprazolam, clonazepam, diazepam and lorazepam), barbiturates, and so-called Z-drugs (e.g., zolpidem, zaleplon and eszopiclone). Used frequently in the past, barbiturate use is now mostly confined to surgical settings, having safety issues for serious withdrawal symptoms (e.g., seizures, delirium, cardiac arrest), drug interactions, risk of coma at high doses, and history as drugs of misuse.

Benzodiazepines have largely replaced barbiturates for the short-term treatment of anxiety,[99] although their own risks for morbidity and mortality include SUD, injuries due to side effects, potentially lethal interactions with other CNS-depressants, and overdose death. In particular patients should be warned not to combine with opioids: Around a third of the United States involve benzodiazepines, with 77% of those deaths also involved opioid analgesics. When not used in combination with other drugs, benzodiazepines are implicated in only 3.7% of drug overdoses.[100] Adverse events associated with benzodiazepine use in older adults include motor vehicle collisions, falls, cognitive difficulties, delirium, sleep disturbances, drug-drug interactions, and impaired function.[101] Side-effects of long-term benzodiazepine use include tachycardia, hypertension, rebound anxiety, agitation, disorientation, hallucinations, and seizures.[102]

In terms of misuse, benzodiazepines produce behavioral disinhibition and amnesia and can enhance opioid-induced euphoria. People who misuse opioids and benzodiazepines together may lose track of how much they have taken and take more. In 2010, 2.2% of Americans misused tranquilizers, mostly benzodiazepines, and nearly 10% of misusers met criteria for a benzodiazepine use disorder.[103]

When comorbid anxiety disorders are severe, psychiatric consultation to establish medication regimen is recommended.[5] In milder cases, no medication may be necessary if adequate behavioral and other nonpharmacologic treatments are helpful.

Behavioral interventions are preferential first-line therapies as it is important to reduce misuse potential. Cognitive behavioral therapy is the psychotherapy with the highest level of evidence.[93] First-line drugs are selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors. Behavioral and SSRI/SNRI therapies have shown superior treatment responses over the long term.[104] Buspirone is another choice and is a frequent adjunct medication[5] but has not found to be effective for panic disorder as a monotherapy.[105] If treatment with SSRIs or SNRIs is not effective, the traditional tricyclic antidepressants such as imipramine and clomipramine may then be considered, bearing in mind that they do have more adverse effects.[93] Particular care is needed when prescribing tricyclics with patients who may be suicidal because the class has heightened risk for toxicity in fatal overdose.[93]

Recommended medications with demonstrated effectiveness in research are escitalopram, paroxetine, and venlafaxine.[95] The benzodiazepines diazepam and lorazepam also showed high effect sizes but are not recommended for routine use.[95] Exercise can be helpful also. In one placebo-controlled trial both clomipramine and exercise led to a significant decrease in panic disorder symptoms, clomipramine earlier than exercise with exercise's effects mainly reducing anticipatory anxiety and panic-related disability.[95]

A benefit of SSRI and SNRI medications is that, unlike benzodiazepines, they can help treat depression when it co-occurs with anxiety.[95] A further benefit of antidepressant therapy is that these medications may be more easily discontinued than benzodiazepines if patients cannot tolerate side effects of jitteriness and nervousness, although patients should be counseled that such symptoms are often short-lived and may be attenuated by a dose reduction or switch in medication.[95] See Table 5 for some suggested medications and doses for specific conditions, remembering the guidelines for first-line therapies already mentioned.[93,105]

Beginning doses are lower than those used to treat depression, and patients who are wary of medication treatment or who have had negative experiences in the past can be initiated at one-quarter usual starting dose.[105] Doses at lower ranges are effective in 75% of patients, but dose adjustments should be individualized and slow, weighing treatment compliance, possible lack of dose optimization, and any interference from psychosocial factors.[93] Treatment for panic disorder may take higher doses (see Table 5 for maximum suggested doses).[105] Clinical experience suggests that 7 days between treatment adjustments is a reasonable duration.[105] A treatment period of 4-6 weeks at a dose considered adequate is usually long enough to tell whether the patient has responded or might benefit from a medication switch.[93]

Some evidence suggests that patients with depression tolerate SSRIs better than SNRIS; however, tolerability is highly individual among patients, and some experience fewer side effects when switched from an SSRI to an SNRI.[93] Some SSRIs and SNRIs are inhibitors of cytochrome P450 enzymes and may interact with other medications.[93] As with any CS that is a CNS-depressant, consider potential additive or synergistic effects with other medications, such as opioids, gabapentinoids, and benzodiazepines.[93] The potential for any such interactions should be monitored.

Benzodiazepines should be prescribed for short-term use only and very cautiously in older adults, who greater risks for falls, cognitive effects, and toxicity from medication interactions.[106]

Table 5. Available Medications for Anxiety Disorders by Condition						
Drug Class	**Medication**	**Indications with RCT Support**	**Starting Dose (for PDA)[a]**	**Typical Therapeutic Daily Dosage**	**Maximum Recommended dose (for PDA)**	**Common Adverse Effects (examples)**
SSRI	Citalopram[b]	PDA SAD	10 mg once daily	20-40 mg	60 mg	Jitteriness, nausea, restlessness, fatigue, increased or decreased appetite, weight gain or loss, tremor, sweating, QTc prolongation, sexual dysfunction, diarrhea, constipation
	Escitalopram[c]	PDA GAD SAD		10-20 mg		
	Fluoxetine	PDA	10 mg once daily	20-60 mg	80 mg	
	Paroxetine	PDA GAD SAD	10 mg once daily	20-50 mg	60 mg	
	Sertraline	PDA GAD SAD	25 mg once daily	50-150 mg	200 mg	
SNRI	Duloxetine	GAD		60-120 mg		Jitteriness, nausea, restlessness, fatigue, increased or decreased appetite, weight gain or loss, tremor, sweating, sexual dysfunction, diarrhea, constipation, urination problems
	Venlafaxine	PDA GAD SAD	37.5 mg once daily	75-225 mg	225 mg	
Tricyclic antidepressant	Clomipramine	PDA		75-250 mg		Anticholinergic effects, somnolence, dizziness, cardiovascular side effects, weight gain, nausea, headache, sexual dysfunction
	Imipramine	PDA	10-25 mg once daily	100-200 mg	300 mg	
Calcium modulator	Pregabalin	GAD SAD		150-600 mg		Dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, constipation, euphoric mood, balance disorder, increased appetite, difficulty with concentration/attention, withdrawal symptoms after abrupt discontinuation
Azapirone	Buspirone	GAD		15-60 mg		Dizziness, nausea, headache, nervousness, light-headedness, excitement, insomnia

RCT = randomized controlled trial
SSRI = selective serotonin reuptake inhibitor
PDA = panic disorder with or without agoraphobia
SAD = social anxiety disorder
GAD = generalized anxiety disorder
SNRI = serotonin norepinephrine reuptake inhibitor
[a] Initiate medication at lowest effective dose, titrate slowly to effect for any anxiety disorder
[b] Do not exceed recommended dose (possible QTc interval prolongation); maximum dose with diminished hepaticfunction 30 mg/daily, for older patients 20 mg/daily.
[c] Do not exceed recommended dose (possible QTc interval prolongation); maximum dose for people over age 65 10 mg/daily

Clinical experience has suggested that clonazepam may be preferred for its slower onset over fast-acting benzodiazepines such as alprazolam and lorazepam, but comparative trials are lacking.[105] Indications could be for the short-term anxiety associated with surgical procedures,[5] when there are contraindications for standard drugs, or in the first few weeks of SSRIs and SSNRIs before efficacy onset.[93]

Patients to be prescribed benzodiazepines for short-term treatment should disclose all medications taken and be evaluated for drug and alcohol current use and history. Using benzodiazepines and alcohol together can increase the risk of overdose death, and the HCP must document and address these factors or risk being held liable for unsafe prescribing practices if he or she has failed to document and address these risk factors.[107]

Chronic daily use of benzodiazepines can lead to a physical dependence that is difficult to address when patients become reluctant to taper or discontinue use.[108] HCPs should monitor patient use as they would any CS and have a plan in place to taper or discontinue. Patients should be counseled to expect withdrawal symptoms when stopping use of benzodiazepines: about a third of patients with long-term use experience withdrawal symptoms within 2 to 10 days of stopping use, and some experience withdrawal during taper to a lower dose. Withdrawal symptoms include hyperarousal symptoms, such as insomnia, anxiety, photophobia, heightened sensitivity to sound, unsteadiness, and seizures.[109] Patients who misuse benzodiazepines are frequently attempting to self-medicate their own anxiety and insomnia symptoms.[110] Patients with a history of benzodiazepine-use disorder or other SUD should not receive benzodiazepines long term.[95]

Insomnia

Insomnia is the most chronic sleep disorder. To be considered chronic insomnia, symptoms must occur at least 3 times per week for at least 3 months and not be better explained by substance or medication use or another disorder.[111,112] Diagnostic criteria for insomnia include difficulty initiating or maintaining sleep, waking up earlier than desired, and resistance to going to bed despite adequate opportunities to sleep.[112]

Additional criteria include one or more of the following daytime symptoms:[112]

- Fatigue or malaise
- Impairments with memory, concentration, or attention
- Negative impacts on social, family, occupational, or academic performance
- Irritability or disturbed mood
- Excessive daytime sleepiness (EDS)

- Hyperactivity, impulsivity, aggression, or other behavioral problems
- Increased risk for errors and accidents
- Lack of motivation or energy

HCPs should screen for psychiatric and medical comorbidities, including sleep apnea, SUD, and stress, and perform a full physical and neurological exam. The patient should be asked about prescribed medications, caffeine and alcohol intake, and any herbal supplements taken.

First-line treatment is cognitive behavioral therapy for insomnia, which is multimodal treatment involving education, stimulus control instructions, time-in-bed restriction, and relaxation training.[113] Patients should be counseled not to use opioids or alcohol to help them sleep.

If nonpharmacologic and non-CS treatments are ineffective, insomnia interferes with function, or insomnia persists despite resolution of the underlying cause, medications may be considered.[114] HCPs should prescribe the lowest effective dose for the shortest possible duration, and avoid prescribing hypnotics for patients with a history of respiratory depression, myasthenia gravis, SUD, or acute cerebrovascular accident. Insomnia medications should be taken shortly before bed and be used in combination with good sleep practices. Patients should be counseled not to drive after taking an insomnia drug. Some common medication choices are as follows:

- Doxepine, which is appropriate for sleep maintenance insomnia and may be useful for patients with contraindications to benzodiazepines or Z-drugs.[115]
- Temazepam, a benzodiazepine used to treat patients who wake up frequently during the night with a peak sedative effect 2-3 hours after ingestion, so that patients must take this medication several hours before bedtime.[116]
- Zaleplon, which stays in the body a short time, making it a good choice for people who try and fail to fall asleep on their own but less optimal for people who tend to wake during the night.
- Zolpidem, which is now available in an extended-release formulation that should not be taken unless the patient is able to get at least 7 to 8 hours in bed.
- Other agents for chronic insomnia that include suvorexant, remelteon, melatonin, and low doses of the sedating antidepressants trazodone and mirtazapine.[117]

Antihistamines facilitate sleep but reduce sleep quality and produce residual daytime drowsiness. Benzodiazepines are commonly prescribed; however, non-benzodiazepine sleep agents are preferred and, if benzodiazepines are used, they are appropriate only for acute insomnia and for intermittent use lasting no longer than 3-4 weeks.[111] Adverse effects for both benzodiazepines and benzodiazepine receptor agonists (i.e., Z-drugs) potentially include anterograde amnesia, complex sleep-related behaviors, falls, cognitive impairment, respiratory depression, and rebound insomnia.[118]

The FDA required a boxed warning on eszopiclone, zaleplon, and zolpidem to alert patients and prescribers that the medications can cause rare but potentially serious complex sleep behaviors that include sleepwalking, sleep driving, and engaging in other activities while not fully awake, such as unsafely using a stove.[119] These behaviors can occur at the lowest dose and in people with no history of such behaviors. In addition, taking sleep medication at night can impair the patient's ability to drive or be fully alert the next day. Patients should be advised not to combine sleep medications with alcohol or other sedating medications and not to exceed the prescribed dose.

BEFORE MOVING ONTO THE NEXT SECTION, PLEASE COMPLETE CASE STUDY 2.

ADHD

Approximately 9.4% of children ages 2-17 years in the United States have ever been diagnosed with ADHD, and nearly a quarter of those with current ADHD have never received treatment.[120]

Boys are more than twice as likely as girls be diagnosed, possibly because hyperactive behaviors are seen more frequently in boys.[120] Most children with ADHD also meet diagnostic criteria for another mental disorder: Boys are more likely to exhibit conditions such as oppositional defiant or conduct disorder, while girls are more likely to have comorbid anxiety or depression.[120]

It was once assumed that ADHD was a childhood disorder that would be outgrown after puberty.[121] Later, this idea was rejected, and it was proposed that ADHD would persist in 35%-60% of cases.[121] Thus, the natural history of ADHD is still not completely understood, and different trajectories may have different vulnerabilities for SUD and for long-term effects of treatment.[121] Within the past 15 years stimulant use has increased significantly in the United States, likely the result of more people being diagnosed with adult ADHD but also reason for increased caution to prevent an emerging public health problem with overdose deaths and misuse involving psychostimulants.[4]

Symptom targets in ADHD are impulsivity, distractibility, poor task adherence, hyperactivity, and lack of attention. Diagnosis is made using criteria of DSM-5, which requires a persistent pattern of inattention and/or hyperactivity-impulsivity.[97] Either presentation can predominate or there may be a combined presentation. For a diagnosis of inattention, at least 6 out of 9 symptoms must have been present for the past 6 months in children younger than 17 years.

Case Study 2

Instructions: Spend 5–10 minutes reviewing the case below and considering the questions that follow.

Ms. Nguyen, a 38-year-old woman, presents with difficulty falling and staying asleep. Her difficulty began within the past 5 months after she was laid off from her retail job of 20 years. She reports no previous problems with sleep but says she is now unable to sleep through the night, awakes unrefreshed, and is drowsy throughout the day. She drinks up to 4 cups of coffee during the day to stay away and focused. She has no history of depression and has never taken a sleep aid with the exception of over-the-counter melatonin, which does not help her stay asleep.

1. **Consider what first-line non-medication therapies to try.** _____

2. **Consider what medication to try, if necessary, and what instructions to give.** _____

3. **Consider what counseling to give the patient regarding sleep hygiene and good habits.** _____

These symptoms must be developmentally inappropriate and disrupt school, work, and social life. HCPs should document the severity of ADHD, ranging from mild to severe, drawing on the number of symptoms and level of social or occupational impairment. HCPs should also rule out any alternative cause such as deafness or cognitive delay.

To make a diagnosis of ADHD in preschool-aged children, clinicians should conduct a clinical interview with parents, examine and observe the child, and obtain information from parents and teachers through DSM-based ADHD rating scales. Symptoms and impairment should be observed in more than one major setting (i.e., social, academic, or occupational), with information obtained primarily from reports from parents or guardians, teachers, other school personnel, and mental health clinicians who are involved in care.

Behavioral and cognitive therapies and other nonpharamcologic treatments are effective in children and adults with ADHD.[122] These therapies should be used preferentially. Preschool-age children and children without severe symptoms benefit solely from behavioral and psychosocial treatments that include evidence-based parent training in behavior management (PTBM). HCPs are encouraged to recommend that parents complete PTBM, if available, before assigning an ADHD diagnosis as PTBM can assist with a variety of problems. Severe ADHD cases benefit from a combination of medication and behavioral interventions.[122]

Dosing should start at the lowest dose and be titrated to clinical efficacy or to intolerance.[122] Medications can cause insomnia and should not be taken close to bedtime. Some formulations are sustained-release to decrease the number of doses taken daily; otherwise, dosing is generally spaced 4-6 hours apart.[122] Stimulants are effective for ADHD and are considered first-line medications with choices described as follows:[120]

- Methylphenidate (ages 6 and older) is the FDA-preferred choice and is available in sustained-release and delayed-release (bedtime) formulations.[122]
- Dexmethylphenidate contains the more pharmacologically active d-enantiomer of racemic methylphenidate and also blocks norepinephrine and dopamine reuptake. It is available in an ER capsule to allow once-daily dosing.
- Dextroamphetamine (ages and 3 and older) and amphetamine mixtures are available in several IR or ER dosage strengths; dextroamphetamine is commonly used first or in case of methylphenidate failure.
- Lisdexamfetamine is an inactive prodrug of dextroamphetamine that elicits CNS stimulant activity and blocks norepinephrine and dopamine reuptake. It is indicated for initial and maintenance treatment of ADHD for ages 6-17 years and adults.
- Amphetamine is a noncatecholamine, sympathomimetic amine that elicits CNS stimulant activity with a precise mechanism producing mental and behavioral effects that remain unclear. Short-acting tablets are dosed 2-3 times daily (ages 3 and older); long-acting once-daily tablets or ER disintegrating tablets are available (ages 6 and older).

Treatment guidelines from the American Academy of Pediatrics on ADHD treatment uphold the central role of medication and behavioral therapies as follows:[120]

- Evaluate for ADHD anyone age 4-18 years who presents with academic or behavioral problems and symptoms of inattention, hyperactivity, or impulsivity
- Screen for comorbid conditions when evaluating for ADHD
- In children ages 4-6 years with ADHD, start evidence-based PTBM and/or behavioral classroom interventions as first-line treatment
- If behavioral interventions do not work, consider methylphenidate
- In children ages 6-12 years with ADHD, prescribe FDA-approved medications for ADHD with PTBM and/or behavioral classroom intervention
- For adolescents ages 12-18 years with ADHD, prescribe FDA-approved medications for ADHD with the adolescent's assent; evidence-based training interventions and/or behavioral interventions are encouraged

HCPs must establish that an adolescent had manifestations of ADHD before age 12.[120] Other considerations with adolescents include that they are more prone to have anxiety and other mood disorders, are at greater risk for SUD than younger children, may feign symptoms to obtain stimulants for performance enhancement, and may have symptoms that mimic ADHD because of marijuana use.[120]

As with any treatment with stimulants, adverse effects can include appetite suppression and weight loss, headaches, and mood effects that include depression and irritability.[122] In addition, stimulants may exacerbate tics in children with underlying tic disorders. It should be noted that amphetamine was associated with a heightened risk of developing new psychosis in adolescents and young adults with ADHD (approximately 1 in 660 patients).[123] Considering 2 million patients received a prescription for amphetamine, this suggests risk of psychosis with amphetamine in thousands of patients. In 2007, the Food and Drug Administration mandated changes to drug labels for stimulants on the basis of findings of new-onset psychosis.[123]

On the other hand, stimulants enhance mental executive functions in people with ADHD.[124] Furthermore, the fear that stimulant therapy will lead to substance abuse, particularly the early exposure in childhood treatment, has not been borne out in long-term studies.[121] High comorbidity between childhood ADHD and subsequent SUD (up to 45%) was neither increased nor decreased by the clinical practice of stimulant medication treatment.

The non-stimulant medication atomoxetine is considered a second-line and, in some cases, first-line medication treatment in children and adults with ADHD.[122] The fact that it is a non-stimulant is considered a benefit. However, studies show it may not be as effective as stimulants.

Other data support use of buproprion or venlaxafine in doses similar to those used to treat depression.[122] Tricyclic antidepressants (e.g., imipramine, desipramine, nortriptyline) are effective in children with ADHD, but adverse effects that include cardiac conduction effects limit their use.[122]

Clonidine and guanfacine have mixed evidence supporting their use, and sudden deaths have occurred in children taking clonidine with methylphenidate at bedtime.[122] It must be emphasized that the etiology of these deaths is unclear. In September 2010, the FDA approved clonidine ER for ADHD as adjunctive therapy to stimulants or as monotherapy.[122] Modafinil has recent placebo-controlled data supporting its efficacy in children with ADHD and may be considered a third- or fourth-line treatment.[122]

Obesity

Approximately 40% of adults and 18.5% of youth had obesity in the United States in 2015-2016.[125] The trend is increasing, but there are some variations in populations: Women had a higher prevalence of obesity than men among non-Hispanic black, non-Hispanic Asian, and Hispanic adults, but not among non-Hispanic white adults.[125] Overall, non-Hispanic black and Hispanic adults and youth had a higher prevalence of obesity compared with other race and Hispanic-origin groups.

Obesity is associated with significant morbidity and mortality.[126] However, there is hope for improvement with weight loss even at modest levels. For example, 5-10% weight loss can decrease the risk of obesity-associated type 2 diabetes, improve lipid levels, and reduce hypertension in a dose-response manner.[127]

Nevertheless, obesity can be challenging to treat, in part because physiological mechanisms cause the body to adapt and resist weight loss. In addition, HCPs must motivate patients to make behavioral and dietary changes necessary to lose and maintain weight while respecting patient autonomy.

Patients evaluated for obesity typically have a general physical exam and health history and calculation of body mass index (BMI). A BMI of 30 or greater is considered obesity. BMI does not measure body fat directly, and bear in mind that the relationship between BMI and body fat varies by sex, age, and race, and Hispanic origin.[125] Morbidity and mortality risk may also vary between different race and Hispanic-origin groups at the same BMI. Among some Asian subgroups, risk may begin to increase at a lower BMI compared with other race and Hispanic-origin groups, although research is inconclusive.[125]

Weight stored around the middle may increase risk of heart disease and diabetes. Risk or presence of diabetes, cardiovascular disease, and hypertension should be ascertained. Blood tests may include cholesterol, liver function, fasting glucose, and thyroid function.

Treatment for obesity includes dietary restrictions or changes, lifestyle intervention, medical management, and surgery. Although not covered in this activity, HCPs should understand when to offer surgical interventions and ensure patients understand the risks and potential benefits of treatment and non-treatment. As with all CS prescribed, a risk-benefit analysis should be performed and the patient monitored carefully. One should also refer the patient for nutrition and other types of consultancy as appropriate as well as support groups and counseling.

The Mayo Clinic suggests considering weight-loss medication if other diet and exercise programs have not worked and one of the following criteria is met:[112]

- BMI 30 or greater
- BMI greater than 27 with co-occurring obesity-related medical complications, such as diabetes, hypertension, or sleep apnea

Medications for weight loss work by suppressing appetite, reducing absorption, or increasing the amount of energy expended.[128] Currently approved medications include short-term use of phentermine, orlistat, phentermine/topiramate, lorcaserin, naltrexone/bupropion, and liraglutide.[129]

Phentermine (Schedule III) is an anorexic agent that works to reduce food intake by causing early satiety. Similar to amphetamine, phentermine interferes with norepinephrine release. A similar drug, sibutramine was linked to heightened cardiovascular and stroke risk and was withdrawn from the market in 2010.

Phentermine/topiramate was approved by the FDA in 2012. Its safety concerns include tachycardia, teratogenicity, metabolic acidosis, psychiatric disorders, and cognitive adverse events.[130] It should not be used in patients with hypertension or coronary heart disease. It also should not be taken by pregnant women because of an increased risk of orofacial clefts in infants exposed during the first trimester of pregnancy.

Narcolepsy

Narcolepsy is a neural dysregulation of the sleep-wake cycle. Research indicates that narcolepsy arises from the interaction of genetic and environmental factors, which lead to an immune-mediated selective loss or dysfunction of orexin (also known as hypocretin) neurons in the lateral hypothalamus.[131]

The classic tetrad of narcolepsy is marked by EDS, cataplexy (brief and sudden loss of muscle tone), hypnagogic (at sleep onset) and hypnopompic (on awakening) hallucinations, and sleep paralysis. The normal rapid eye movement (REM) sleep cycle is disrupted and people with narcolepsy may fall asleep suddenly during the day as well as experience such symptoms as vivid dreams, vivid hallucinations that may be visual, auditory, or tactile in nature, and total paralysis immediately before falling asleep or after waking. The chief feature of narcolepsy is EDS, which must be present at least 3 months to justify the diagnosis. Cataplexy is present in 70% of people with narcolepsy[132] and, if present with EDS, is strongly suggestive of narcolepsy.

A version of the HLA-DQB1 gene called HLA-DQB1*06:02 increases the risk of developing narcolepsy, particularly in people who also have cataplexy.

Pediatric narcolepsy has a typically different clinical presentation. Rarely do children display all 4 of the classic tetrad of narcolepsy symptoms. Instead of classic cataplexy, they may display a range of motor disturbances with a predominance of restlessness and motor over-activity and are frequently inattentive and display emotional lability. Children with narcolepsy are at risk for being misdiagnosed with ADHD, a learning disability, depression, or other disorder.

The Epworth Sleepiness Scale (ESS) is a frequently used self-administered questionnaire to assess for daytime sleepiness. A score from 0-24 is possible with 10 or higher warranting further investigation. The scale has high specificity (100%) and sensitivity (93.5%) in narcolepsy.[133] The scale can be found here: http://epworthsleepinessscale.com/about-the-ess/

Diagnosing narcolepsy requires a physical examination to rule out other neurological conditions and a detailed medical history.[134] An overnight polysomnogram is performed to reveal whether REM sleep occurs early in the sleep cycle and to rule out other conditions such as sleep apnea.[134] This is followed by a multiple sleep latency test to assess for daytime sleepiness by measuring how quickly a person falls asleep and whether they enter REM sleep.[134] During this test, the patient takes 5 short naps separated by 2 hours. If the patient falls asleep in less than 8 minutes on average, this indicates EDS. Furthermore, if REM sleep happens within 15 minutes at least twice during testing (including the sleep study the night before), this abnormality is strongly suggestive of narcolepsy.

When necessary, additional biomarkers helpful to confirm diagnosis are orexin deficiency in the cerebrospinal fluid and positivity for HLA-DQB1*06:02.[131] Patients with narcolepsy type 1 have cataplexy and little or no orexin in cerebrospinal fluid; narcolepsy type 2 is a diagnosis of exclusion requiring ancillary tests ruling out other causes of EDS.[131]

Narcolepsy has a major effect on the patient's quality of life and makes functioning in life roles difficult.[135] Treatment for narcolepsy should have medication and non-medication components with sleep hygiene being a paramount consideration.[136] Most people with narcolepsy have trouble sleeping at night. A regular sleep schedule is important to help patients improve, and daytime naps may also be helpful.[137]

Fortunately, treatment with stimulant and anticataleptic drugs are usually effective.[131] Stimulant medications have been shown to improve daytime sleepiness in 68-85% of patients. Stimulants increase wakefulness, vigilance, and performance and are believed to alter midbrain dopaminergic activity, but the precise mechanism of action is unknown. Cataplexy treatments act symptomatically, and there is no evidence suggesting that they target the orexin system.[138]

Common pharmacologic treatment options for narcolepsy are discussed as follows:

- Modafinil (a Schedule IV drug) is generally considered first-line treatment over older stimulants. It does not appear to involve altering levels of dopamine or norepinephrine, affect total sleep time, or suppress REM sleep. In a meta-analysis of 9 randomized controlled trials including 1054 patients, modafinil was significantly beneficial in eliminating EDS and decreasing sleep attacks, naps, and somnolence when compared with placebo but did not diminish cataplexy attacks.[135] Nausea was more common with modafinil than placebo but less common than with sodium oxybate.[135]
- Amodafinil is an enantiomer of modafinil with fewer side effects, indicated for the treatment of EDS.[136] The most common adverse effects are headache, nausea, dizziness, and difficulty sleeping. Its safety has not been established in children younger than 17 years.
- Methylphenidate (Schedule II) or other stimulant drugs may be tried if modafinil is not effective, but treatment must be carefully monitored due to side effects and misuse risk.[134] Methylphenidate has been prescribed more than any other choice and is shown to improve sleep tendency.[136] A difficulty is that methylphenidate can also affect night-time sleep. Other side effects include headache, GI symptoms, irritability, and nervousness, and disturbances in heart rate.[134] Cardiovascular side-effects can be serious, including cardiac arrhythmias, hypertension, angina, and circulatory collapse. Amphetamines should not be prescribed or administered to patients with cardiovascular disease or who are taking MAO-inhibitors. Lastly, patients taking amphetamines may experience anorexia, nausea, vomiting, abdominal pain, or diarrhea. Chlorpromazine, an alpha-blocker, is the antidote for amphetamine overdose.
- Sodium oxybate (Schedule III) is the only FDA-approved treatment for cataplexy and is also used to treat EDS.[136] It restores sleep continuity, decreases hallucinations, and reduces sleep paralysis. Sodium oxybate must be administered twice per night because of its short half-life, and dose titration can be challenging. Side-effects include nocturnal confusion, sleepwalking, dizziness, nausea and enuresis. Sodium oxybate should not be used with alcohol or other CNS depressants. SUD with sodium oxybate is rare,[139] but fatal respiratory depression is possible with overdose.
- Solriamfetol, a dopamine/norepinephrine reuptake inhibitor, was FDA-approved in 2019 to improve wakefulness for EDS in patients with narcolepsy. It is in a class of wakefulness-promoting agents and appears to work by increasing substances in the brain that control sleep and wakefulness. Solriamfetol was placed in Schedule IV.

- Pitolisant is a nonscheduled first-in-class histamine3 (H3) receptor antagonist/inverse agonist approved in 2018 for EDS.
- Antidepressants are frequently prescribed off-label to reduce cataplexy; however, one meta-analysis found no good-quality evidence that antidepressants improve this symptom or improve quality of life.[140] Antidepressant therapy can be considered second-line therapy behind sodium oxybate for cataplexy, in particular, clomipramine and venlafaxine[138]

Currently, there is no FDA-approved drug for children with narcolepsy; however, the medications used to treat narcolepsy in adults have been used off-label in the pediatric population with positive results, particularly methylphenidate and modafinil in patients ages 6–15.[136]

Patients vary considerably in the dosage required to alleviate ED. In some patients, daytime sleepiness is completely relieved with methylphenidate 5 mg/day, while in others, higher dosages are required. HCPs should initiate treatment at low dosages and individualize therapy as appropriate in accordance with a patient's distinct needs and symptoms.

Patients should be monitored regularly for response to treatment and side effects. It is recommended that visits happen at least annually and, if a patient is on a stimulant, every 6 months.[136] Further recommended steps are to coordinate care with a sleep specialist, when available, and to advise the patient to contact narcolepsy support groups.

Pain

Patients need access to appropriate and effective pain relief with a commitment to avoiding or managing adverse effects arising from treatment with CS. Some 50 million U.S. adults live with chronic daily pain, and 19.6 million experience high-impact pain that interferes with daily life and work.[5] Patients who suffer pain long term have reduced quality of life and are at risk for morbidity when pain goes untreated or is managed inappropriately. Effective pain management skills are part of quality medical practice.

Effective treatment for pain does not usually involve ongoing opioid therapy, which should be reserved for patients with pain severe enough to warrant an opioid and for whom more conservative therapies would not be effective or have previously failed to be effective.[13] Numerous non-opioid pharmacologic therapies are available for pain, and these should be tried or considered, alone or in combination, before initiating long-term opioid therapy.[5] A trial of opioids, when indicated, should be part of a comprehensive treatment approach, typically in combination with one or more treatment modalities.[37] Other CS that are CNS depressants are commonly prescribed to patients in pain in combination with opioids (e.g., benzodiazepines, antidepressants, gabapentinoids), and the potential for misuse of combinations, SUD, overdose death, drug interactions, and diversion must be managed though responsible prescribing and monitoring practices.

To manage neuropathic pain well generally requires combining pharmacologic and nonpharmacologic approaches.[141] Along with gabapentinoids, medications that provide the most relief include antidepressants and local anesthetics.[141] Nonsteroidal anti-inflammatory drugs (NSAIDs) are not considered effective treatments for neuropathic pain.[13,141]

Guidelines and Screening

Several clinical practice guidelines are available to assist HCPs in appropriate prescribing of opioid analgesics,[13,35,37-39] and individual states also publish guidelines.[142] The CDC guideline is intended for pain not associated with cancer, end-of-life, or palliative care.[13]

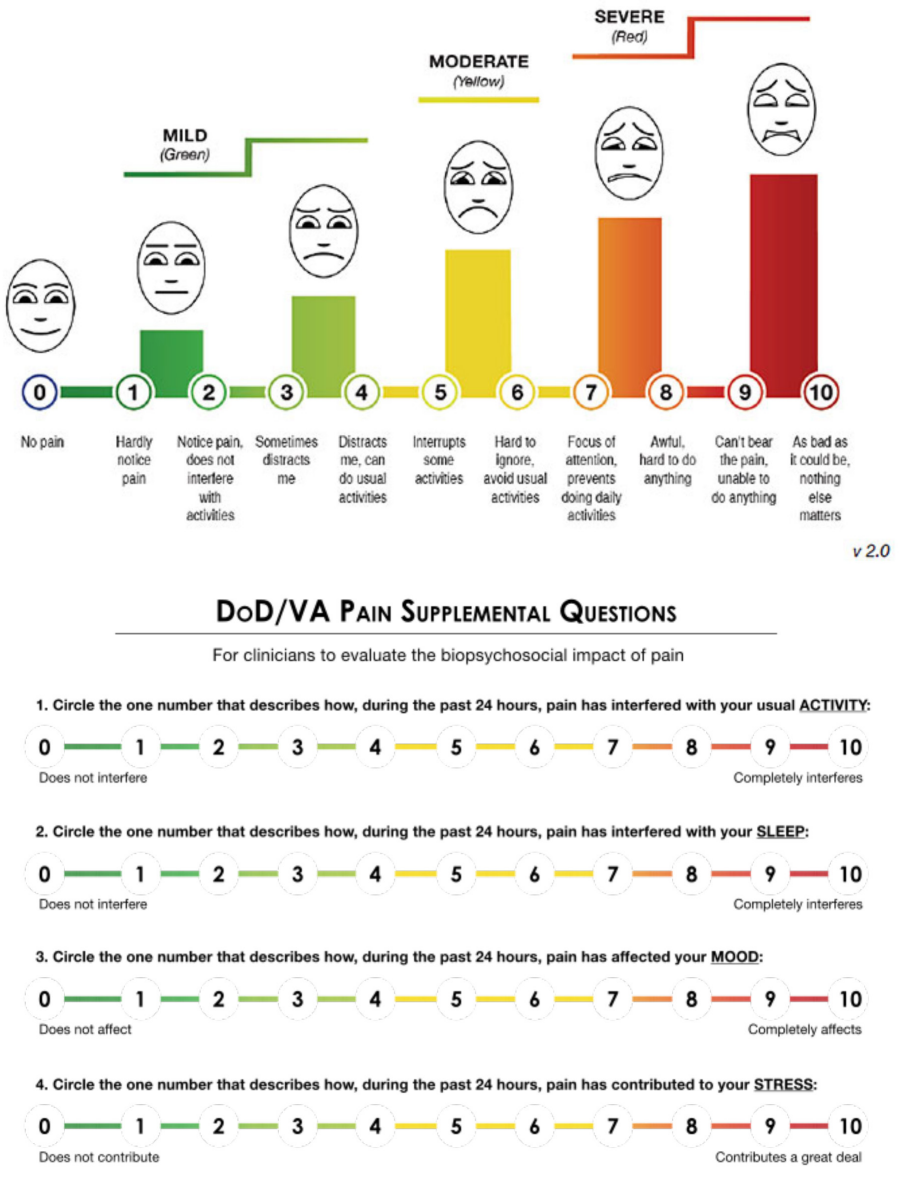
Clinical practice tools to assist pain assessment include:

- The Visual Analogue Scale (VAS) and Numerical Rating Scale (NRS)[143]
- The Brief Pain Inventory[144,145]
- The Pain, Enjoyment of Life, and General Activity Scale[146]
- The McGill Pain Questionnaire[143]
- The Multidimensional Pain Inventory[147,148]
- The Defense and Veterans Pain Rating Scale (Figure 3).[5,149]

The clinical interview should include risk evaluation for development of SUD with the use of CS for pain management. Factors that contribute to risk are many and include the following:[5,150-152]

- Younger age (<30 years)
- Personal history of substance misuse
- Adverse social and life circumstances
- Comorbid mental conditions
- Social exposure to others with SUD
- Exposure to parental SUD
- History of trauma or childhood adversity
- Obtaining CS from more than one HCP without authorization
- Obtaining multiple CS from multiple sources

Figure 3. The Defense and Veterans Pain Rating Scale and Supplemental Questions[108]



- Use of illicit street drugs during therapeutic treatment with CS
- Sleep disturbances
- Mood disorders
- Stress

Screening tools to assist in assessing for the risk of OUD may also be useful when prescribing other CS. These include the Opioid Risk Tool,[153] Revised Screener and Opioid Assessment for Patients with Pain,[154] Pain Medication Questionnaire,[155] and the brief CAGE-AID (Adapted to Include Drugs).[156] Even single questions, such as, "How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?" can be effective means of screening for misuse.[157]

Mental health screening is important because comorbid psychiatric conditions often co-occur with chronic pain and can influence the chance for therapeutic success.

Clinical mental health screening tools include:
- Patient Health Questionnaire-2 (PHQ-2) for depressive disorder that leads to more detailed assessment if either item is positive.[158]
- Patient Health Questionnaire-9 may be used initially or as a follow-up to the PHQ-2.[159]
- Beck Depression Inventory-II[160]
- Suicidal ideation is addressed by items on the PHQ-9 and BDI-II.
- Beck Anxiety Inventory[161]
- The Generalized Anxiety Disorder-7 and GAD-2 are validated and recommended to assess for generalized, panic, and social anxiety disorders, and PTSD.[13,162,163]

Risk factors for overdose in people taking opioids include:[53,164-167]
- Middle age
- History of substance abuse
- Comorbid mental and medical disorders
- High opioid dose (although risk is present at any dose)
- Recent upward titration
- Recent opioid rotation
- Methadone
- Benzodiazepines
- Antidepressants
- Unemployment
- Polysubstance abuse
- Recent release from prison
- Recent release from abstinence-based addiction treatment
- Sleep apnea
- Heart or pulmonary complications (e.g., respiratory infections, asthma)
- Pain intensity

Acute Pain

Opioids in acute pain settings should only be prescribed for the duration of the pain at the lowest effective therapeutic dose.[13,168] Prescriptions beyond 3 days are rarely necessary,[13] while more severe episodes rarely need more than 7-14 days, although there are exceptions, and each patient should be treated as an individual.[13,82] Be aware also that localities and states may have strict regulations governing maximum duration of prescriptions for acute pain. Acute pain should not be treated with ER/LA formulations of opioids, and opioids typically are not recommended for nonspecific back pain, headaches, or fibromyalgia, if the HCP should see a patient experiencing acute pain flares with these conditions.[37] HCPs should check the PDMP ahead of prescribing opioids for acute pain whenever possible[5] and reevaluate the pain diagnosis and treatment plan if pain persists beyond the expected healing period.

Chronic pain

Prior to beginning treatment for chronic pain, the goals concerning pain relief and improved function should be ascertained and discussed with the patient. The risk-benefit analysis performed initially in deciding whether opioids are the right treatment should be ongoing as the HCP monitors progress toward these goals.

Fundamental tenets of chronic pain management include the following:[13,37,38,42,169,170]
- Complete a full patient evaluation and assessment to verify the need for CS medication
- Request the patient's prescription history from the state PDMP before prescribing opioids and periodically thereafter, from every prescription to every 3 months (check state laws)[2]
- Perform initial UDT and consider testing every patient at least once annually, higher-risk patients 2-3 times annually (check state laws)[2]
- Ask about all medications a patient is taking and why
- Discuss pregnancy status or plans with patients who are taking opioids and counsel them on the risks
- Use relevant screening instruments (e.g., pain, substance abuse, mental health, condition-specific tests)
- Create individualized treatment plans
- Prescribe opioids only if alternative therapies do not deliver adequate pain relief
- Have the patient sign informed consent and a treatment agreement and retain in record
- Set and document treatment goals
- Perform and periodically reevaluate risk-benefit analysis
- Follow-up with patients frequently (within 1-4 weeks of initiation or dosage change and at least every 3 months thereafter, as advised by the CDC).[13]
- Educate patients to risks vs benefits of all treatments
- Manage medications, avoiding harmful interactions and combinations
- Monitor the patient for adherence to the treatment regimen
- Have an exit strategy in place to taper humanely and collaboratively
- Vigilantly document all clinical actions in the patient medical record
- Counsel patients regarding any nonadherence and progress toward treatment goals
- Obey all CS prescribing regulations
- Keep current all DEA-registrant requirements

Functional goals should be meaningful to the patient and might include:
- Progress in physical therapy
- Better sleeping patterns
- Increased activities of daily living
- Return to work
- Increased social activities
- Regular exercise

Informed consent outlines the risks of the therapy and the adverse events that are likely or possible. Treatment agreements pertaining to opioids frequently include instructions such as:[35]
- To take only as directed
- To agree to initial, periodic, and random UDT
- To understand PDMP will be checked
- To agree to use only one pharmacy and one prescription provider
- To agree to no replacement medications (at HCP discretion)
- To agree to no early refills (at HCP discretion)
- To safeguard CS medications from others, dispose of properly
- Patient education as to the potential risks of medications as well as sought benefits
- Reasons the treatment plan involving CS might change or be discontinued
- The clinic's policies and the HCP's expectations that the patient will adhere to the terms of treatment.

HCPs should counsel patients as to the purpose for UDT, disclose what actions could be expected based on results, and discuss the cost to the patient. Be clear that patients should disclose any other prescriptions or drugs or any kind that they are using, including the time and last dosage amount of any CNS-depressant drug.

The frequency and intensity of monitoring measures should increase with evidence of heightened risk for misuse, but all patients have some risk when taking CS on an ongoing basis. Mental health and suicide risk are topics to discuss with the patient and to document the outcome of all referrals and decisions taken.[171]

Naloxone co-prescription is recommended with patients at higher risk of opioid overdose. This includes those with a history of overdose, history of SUD, clinical depression, opioid dosages ≥50 MME/day, concurrent benzodiazepine use,[13] or with evidence of increased risk by other measures.

Initiating Opioids

Patients initiated on a trial of opioids for chronic pain should be initiated at the lowest effective dose and titrated slowly to analgesic effect.[38] Short-acting (SA) opioids are preferred and considered safer when initiating a therapeutic trial of opioids and are often prescribed for use as needed, every 4 to 6 hours.[38,172]

If patients require long-term treatment and pain is severe enough to require around-the-clock, long-acting (LA) analgesia that is not adequately relieved by IR/SA opioids or other therapies, consider a transition to ER/LA opioids with scheduled dosing.[173]

Methadone for pain presents special clinical challenges due to properties that include a long and variable half-life and pain relief that wanes even though the concentration in the body remains and depresses breathing.[26] Only HCPs with experience and knowledge of methadone should prescribe it (only for severe pain unrelieved by other opioids) or else seek expert consultation.[85] Dual-mechanism opioids may control pain with less opioid, and opioid-sparing techniques, such as combining therapeutics should be considered.

Contraindications for initiating long-term opioid therapy include hypersensitivity to active ingredients, significant respiratory compromise, acute or severe bronchial asthma, known or suspected paralytic ileus and GI obstruction, and diversion of CS.[37]

Clear rationale for prescribing or increasing dosages of opioids should be documented in the medical record, particularly if dosages exceed current recommended guidelines.[35] The CDC guideline identified a dose limit of 90 morphine milligram equivalents (MMEs) daily after which caution is advised.[13] However, no dose is completely safe,[174] and much of the risk at higher doses appears to be associated with co-prescribed benzodiazepines.[53] Evidence is strong that prescribing opioids together with benzodiazepines increases risk for overdose,[37,175] and evidence also suggests that co-prescription of opioids and gabapentinoids may increase overdose risk.[37]

After treatment begins, adjust the dose and other components of therapy to the patient's individual needs, utilizing non-opioid treatment modalities whenever possible. Items to evaluate and document include analgesia, daily activities, adverse effects, aberrant drug-related behaviors, cognition, function, and quality of life.

Patient education is important and also pertains to treatment with other CS as well as opioids. Informed consent and treatment agreements are useful documents to facilitate discussions with patients around the various risks of any CS treatment such as tolerance, physical dependence, SUD, and overdose that could lead to death.

Patients should be counseled to safely use, store, and dispose of medications, keeping them out of the hands of children, visitors to the home, family members, or others who might wish to obtain pills for diversion or could be harmed by accidental ingestion (this last includes pets in the home). HCPs should explain their facility's policies regarding UDT screenings, pill counts, and PDMP checks, and clarify that monitoring measures are to ensure that treatment remains safe and no harmful usage or SUD develops.

HCPs should discuss that cessation of CS prescriptions will be accomplished, when necessary, with the cooperation of the patient and because the treatment is no longer necessary or has become harmful. They should also attempt to get the patient to understand that treatment for pain is not synonymous with treatment with opioids or any other CS.

Documentation must be complete and legible and should include should include the items shown in Table 6.[13,18,35,37-39,82] Please take a moment to study the table, then read through the case example that follows.

BEFORE MOVING ONTO THE NEXT SECTION, PLEASE COMPLETE CASE STUDY 3 ON THE NEXT PAGE.

Recognizing Substance-Use Disorder

The American Society of Addiction Medicine (ASAM) refined its definition of addiction in 2019. Its brief description may help HCPs view the condition as the "treatable, chronic medical disease" that it is, one which involves "complex interactions among brain circuits, genetics, the environment, and life experiences."[176] The ASAM further described how behaviors become compulsive and often continue despite harmful consequences and suggested that prevention and treatment generally succeed on a par seen with other chronic diseases.[176]

Clinically, an SUD is diagnosed using DSM-5 criteria; OUD is specified if opioids are the drugs used (Table 7).[177,178] A minimum of 2-3 criteria are required for a mild OUD diagnosis, while 4-5 is moderate, and >6 is severe. Addiction, while not a DSM-5 diagnosis, is a frequently used term and typically describes severe SUD. The presence of tolerance and physical dependence does not contribute to the diagnosis of OUD if opioids are prescribed and the patient takes the medication as prescribed.

When evaluating a patient and during periodic clinical follow-up, it is important to watch for signs and symptoms of dangerous non-adherence with treatment directives. One such important characteristic is obtaining CS prescriptions from more than one prescriber, sometimes at multiple facilities (aka "doctor shopping") although the patient has agreed to use only one prescriber and one pharmacy to fill all CS prescriptions.[32,179] Other indicators of continuing non-adherence to medical direction include taking too much medication, taking medication by the wrong route of administration, use of illicit substances, and use of unauthorized prescription drugs obtained from nonmedical sources. In addition, pay attention if the patient exhibits ongoing problems with interacting and fulfilling roles related to family, work, and personal life.

Table 6. Items to Perform and Document in the Patient Record When Prescribing Opioid Therapy for Chronic Pain[20,61,77,85,138,141]

1. Signed informed consent
2. Signed opioid treatment agreement(s)
3. Pain and medical history
   - Chief complaint
   - Treatments tried and patient response
   - Past laboratory, diagnostic, and imaging results
   - Comorbid conditions (e.g., medical, substance-use, psychiatric, mood, sleep)
   - Social history (e.g., employment, marital, family status, substance use)
   - Pregnancy status or intent, contraceptive use
4. Results of physical exam and new diagnostic and imaging tests
   - Review of systems
   - Pain intensity and level of functioning
   - One or more indications for opioid treatment
   - Objective disease/diagnostic markers
5. Results of opioid risk assessment prior to prescribing opioids
   - Clinical interview or any screening instruments
   - Personal history of SUD, mental health disorder
   - Family history of SUD, mental health disorder
   - Co-management or treatment referral for patients at risk for SUD
   - Treatment or referral for patients with active OUD
   - Treatment or referral for patients with undiagnosed depression, anxiety, other mental health disorders
6. Treatment goals for pain relief, function, quality of life
7. Treatments provided
   - With risk-benefit analysis after considering available nonpharmacologic and non-opioid pharmacologic op&ons
   - All medications prescribed (including the date, type, dose, and quantity)
   - All prescription orders for opioids and other controlled substances whether written or telephoned
8. Prescription of naloxone, if provided, and rationale
9. Results of ongoing monitoring toward pain management and functional goals

SUD = substance-use disorder OUD = opioid-use disorder; PDMP = prescription drug-monitoring programs; UDT = urine drug testing

Case Study 3

Instructions: Spend 5–10 minutes reviewing the case below and considering the questions that follow.

Mr. Connors, 54, has chronic neck pain for which he is prescribed short-acting 10 mg hydrocodone/ACET to take as-needed up to 4 per day. He does not take this medication daily but only on days when the pain spikes to 7/10 at rest, usually after exertion such as weeding his flower bed or taking a bike ride. He has always had consistent UDTs and PDMP checks, and the hydrocodone prescription helps him meet his goals of an active life. He drinks 2 beers several evenings a week and has no other history of or current substance use. He is treated for depression and has been stable on his escitalopram dose for years. His HCP and he have discussed the wisdom of limiting alcohol use with his current medications, and he has promised to try. While mowing his lawn one weekend, he strains his neck more than usual and is in significant pain that is constant, throbbing, and intense (9/10). He ices the area and takes 800 mg ibuprofen but finds the pain is still so intense he cannot sleep that night. His grown daughter offers him one of her alprazolam 1 mg, and he accepts so that he can sleep.

1. **Consider what would be the responsibility of the prescriber of CS in such a scenario.**_____

2. **Consider the components of the treatment agreement previously assigned.**_____

3. **How would one appropriately counsel and follow-up with the patient?**_____

Table 7. Criteria for Opioid-Use Disorders from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition[92]

A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:
• Opioids are often taken in larger amounts or over a longer period of time than was intended
• There is a persistent desire or unsuccessful efforts to cut down or control opioid use
• A great deal of time is spent in activities to obtain the opioid, use the opioid, or recover from its effects
• Craving, or a strong desire or urge to use opioids
• Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home
• Continued opioid use despite having persistent or recurrent social or interpersonal problems caused by or exacerbated by the effects of opioids
• Important social, occupational, or recreational activities are given up or reduced because of opioid use
• Recurrent opioid use in situations in which it is physically hazardous
• Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that's likely to have been caused or exacerbated by the substance
• Tolerance,* 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
• Withdrawal,* as manifested by either of the following: a. The characteristic opioid withdrawal syndrome b. The same—or a closely related—substance is taken to relieve or avoid withdrawal symptoms
*This criterion is not met for individuals taking opioids solely under appropriate medical supervision. Severity: mild = 2–3 symptoms; moderate = 4–5 symptoms; severe = 6 or more symptoms.

Trips to the emergency department (ED) are concerning, particularly if CS are requested there and this type of medical care utilization becomes a pattern that repeats. Data show a correlation of patients frequently obtaining opioids in EDs with "pill shopping" in that 5% to 10% are already taking opioids from other providers.[18]

Benzodiazepine SUD may present with particular physical signs that include:[180]

- Speech problems
- Incoordination
- Dizziness
- Disorientation
- Poor memory
- Inability to concentrate
- Sedation
- Decreased blood pressure
- Decreased respirations
- Coma

As with other SUD, behavioral difficulties may include relationship conflicts, poor school or work performance, financial and/or legal issues, multiple prescribers, early medication refills, and use of the medication (in this case, benzodiazepine) together with other CNS-depressant drugs.[180]

Any misuse can threaten the integrity of CS therapy if not addressed. Not all misuse is intentional; for example, taking an incorrect dose.

Similarly, not every instance of failure to comply with medical direction indicates an SUD has developed in the patient who has lent medications to a family member or taken an extra pill. However, repeated failure to adhere to the treatment agreement along with increasingly dangerous patterns of usage call for action on the part of the HCP. These actions might include a switch to less risky treatments or medications to manage symptoms of the medical condition for which the CS was prescribed. Referral to specialists in pain, SUD treatment, or mental health may be indicated. In some cases, the patient may need to be referred entirely for specialist management and, in other cases, co-management of the patient with a specialist or specialists may be possible and advisable. If, after a risk-benefit analysis, it appears CS should be tapered, it is important to do so carefully and safely.

Tapering Controlled Substances

Tapering to reduce a long-term opioid dosage or to discontinue opioid therapy can be done for the following reasons:[181]

- Patient has requested to discontinue or taper doses
- Pain improves
- A new treatment is expected to improve pain
- Pain and function are not meaningfully improved with opioids
- Patient is receiving higher opioid doses without evidence of benefit
- Patient has current evidence of opioid misuse
- Patient experiences side effects that diminish quality of life or impair function
- Patient experiences overdose or other serious event (e.g., hospitalization, injury) or has warning signs (e.g., confusion, sedation, slurred speech) for an impending event
- Risk for adverse outcomes is increased through co-administration of medications (e.g., benzodiazepines) or medical conditions (e.g., lung disease, sleep apnea, liver disease, kidney disease, fall risk, advanced age)
- Long-term opioid administration has been prolonged (e.g., years) and current benefit-harm balance is unclear

HCPs should attempt to be patient-centered, get patient buy-in to a tapering plan, and make sure the patient understands that being treated with CS comes with responsibility. In considering whether opioids or other CS continue to meet treatment goals, evaluate risks versus benefits and avoid insisting on tapering or discontinuation when opioid use may be warranted (e.g., treatment of cancer pain, pain at the end of life, or other circumstances in which benefits outweigh risks of opioid therapy). HCPs should know that the CDC guideline for prescribing opioids was not intended to mandate discontinuance of opioids when they are indicated, though a clear evaluation of risks versus benefits should be documented for patients prescribed high-dose opioids. The guideline's 90 MME/day dosage threshold should not be misinterpreted as a mandate to reduce current dosages but as an opportunity consider individual patient situations.[181]

HCPs should avoid dismissing patients from care. Instead, refer patients for medication treatment for OUD (MOUD) as described below and ensure that patients continue to receive coordinated care.[181] Patients who are discontinued or tapered non-collaboratively are at risk for acute withdrawal, pain exacerbation, anxiety, depression, suicidal ideation, self-harm, ruptured trust, opioid overdose, and seeking opioids from high-risk sources.[5,181,182]

Taper without the patient's consent is a challenging situation and the risks versus benefits of treatment should be clearly defined. If the prescriber makes a determination that the risks of the treatment outweigh the benefits, the prescriber may need to recommend taper. One should continue to treat pain and withdrawal with pharmacologic and nonpharmacologic options. If the patient has serious mental illness, a high suicide risk, or suicidal ideation, offer or arrange for consultation with a behavioral health provider before initiating a taper.[181] Treating common comorbid mental disorders (e.g., depression, anxiety, and PTSD) can improve the likelihood of opioid tapering success and reduce dropouts.[181]

Access appropriate expertise if considering opioid tapering or managing OUD during pregnancy.[181] Opioid withdrawal risks include spontaneous abortion and premature labor. For pregnant women with OUD, MOUD is preferred over detoxification.

HCPs should advise patients that there is an increased risk for overdose on abrupt return to a previously prescribed higher dose.[181]
One should strongly caution them that it takes as little as a week to lose tolerance. Patients should be provided with opioid overdose education and possibly offered naloxone.

Taper should be slow enough to minimize opioid withdrawal, and longer duration of therapy entails slower taper (common tapers involve dose reductions of 5% to 20% every 4 weeks). Slower tapers (10% per month or slower) can be completed over months or years with long intervals between dose reductions and the possibility of pauses to adjust to a new dose.[181] When opioid use has lasted weeks or months rather than years, faster tapers may be appropriate. A decrease of 10% of the original dose per week or slower (until 30% of the original dose is reached, followed by a weekly decrease of 10% of the remaining dose) can be successful for some patients.[181] More rapid tapers (e.g., over 2-3 weeks) might be needed for patient safety when the risks of continuing the opioid outweigh the risks of a rapid taper, as in the case of a severe adverse event such as overdose.

Signs of withdrawal with opioids occur when stopping or decreasing doses or administering an opioid antagonist. Acute opioid withdrawal symptoms include drug craving, anxiety, restlessness, insomnia, abdominal pain or cramps, nausea, vomiting, diarrhea, anorexia, sweating, dilated pupils, tremor, tachycardia, piloerection, hypertension, dizziness, hot flashes, shivering, muscle or joint aches, runny nose, sneezing, tearing, yawning, and dysphoria.[181]

Pain often worsens with withdrawal and, although the pain may be prolonged, it does tend to diminish over time for many patients.[181]

If patients on high opioid dosages are unable to taper despite worsening pain and/or function, whether or not OUD criteria are met, HCPs may consider transitioning to buprenorphine. Buprenorphine is a partial opioid agonist that can treat pain as well as OUD, result in less opioid- induced hyperalgesia (i.e., heightened pain response), and easier withdrawal than full mu-agonist opioids, and less respiratory depression than other LA opioids.[181]

Treatments for withdrawal symptoms include alpha-2 agonists clonidine and lofexidine.[181] Other medications may be NSAIDs, ACET, or topical menthol/methyl salicylate for muscle aches; trazodone for sleep disturbance; prochlorperazine, promethazine, or ondansetron for nausea; dicyclomine for abdominal cramping; and loperamide or bismuth subsalicylate for diarrhea.[181]

Some patients are taking opioids and benzodiazepines concurrently, and one or both medications are to be tapered. Although tapering may be accomplished more rapidly in a controlled setting like a detox unit, benzodiazepines must be tapered gradually in the outpatient setting due to risks of withdrawal that include anxiety, hallucinations, seizures, delirium tremens, and, in rare cases, death.[181] Long-acting benzodiazepines should be slowly discontinued over several months.[56] If needed, gabapentinoids, carbamazepine, or valproic acid may help facilitate self-managed reduction or normalize sleep, reflexes, and anxiety.[55,183-186] A benzodiazepine tapering flow sheet is available here: https://www.oregonpainguidance.org/app/content/uploads/2016/05/Opioid-and-Benzodiazepine-Tapering-flow-sheets.pdf.

Treating Opioid-Use Disorder

At least 2.35 million people in the United States have OUD involving prescription opioids, illicit opioids such as fentanyl and heroin, or a combination of these.[19] Yet over 70 percent of people who needed treatment for OUD in 2017 did not receive it.[19] The recommended evidence-based treatment for OUD is MOUD, which is treatment with medication combined with behavioral counseling and such services as case management and peer support. FDA-approved medications for OUD are methadone, buprenorphine, and extended-release naltrexone. MOUD relieve the withdrawal symptoms and psychological cravings and are safe to use for months, years, or even a lifetime.

Patients who are suffering with OUD (or another SUD involving a CS) need encouragement to seek treatment and reassurance that they are not trading "one addiction for another," which is a common misperception. Research shows that people treated with opioid agonist medications are less likely to die from overdose or otherwise prematurely, are more likely to remain in treatment, have improved social functioning, and are less likely to inject drugs and transmit infectious diseases.[19]

In pregnant women with OUD, the risk of opioid exposure from opioids used to treat OUD should be discussed and balanced against the risk of untreated OUD, which might lead to illicit opioid use associated with outcomes such as low birth weight, preterm birth, or fetal death.[187]

Provision of MOUD in a clinic setting is regulated by the federal government. Oversight of MOUD remains a multilateral system involving states, the Substance Abuse and Mental Health Services Administration (SAMHSA), HHS, the Department of Justice, and the DEA. SAMHSA's Division of Pharmacologic Therapies, part of SAMHSA's Center for Substance Abuse Treatment, manages the day-to-day oversight activities.

HCPs need a separate DEA registration to treat OUD with methadone (a Schedule II drug).[24] Use of buprenorphine/naloxone (a Schedule III drug) to treat OUD no longer requires specific training, but a waiver from the DEA is required to prescribe, administer, or dispense it.[24] Practitioners are encouraged to receive training prior to use of buprenorphine, and new short trainings are freely available (see the following link): https://elearning.asam.org/products/buprenorphine-mini-course-building-on-federal-prescribing-guidance#tab-product_tab_overview. Recent practice guidelines released by the Substance Abuse and Mental Health Services Administration within HHS are available here: https://www.samhsa.gov/newsroom/press-announcements/202104270930.

If an HCP is unable to treat the patient in need of addiction treatment, existing facilities can be found through the following websites:

- Opioid Treatment Program Directory: https://dpt2.samhsa.gov/treatment/directory.aspx
- SAMHSA's Behavioral Health Treatment Services Locator: https://findtreatment.samhsa.gov/
- SAMHSA's Buprenorphine Treatment Physician Locator: https://www.samhsa.gov/medication-assisted-treatment/practitioner-program-data/treatment-practitioner-locator
- SAMHSA's National Helpline – 1-800-662-HELP (4357): https://www.samhsa.gov/find-help/national-helpline
- Substance Use Treatment Locator (FindTreatment.gov): https://findtreatment.gov/

A number of measures have been aimed at increasing access to buprenorphine. Federal regulations and legislation related to OUD treatment include the following:[188]

- The Code of Federal Regulations provides for certification in using CS to treat OUD in opioid treatment program (OTPs) overseen by SAMHSA; MOUD patients receiving care in OTPs are also required to receive counseling.
- The Drug Addiction Treatment Act of 2000 (DATA 2000) permits physicians who meet certain qualifications to treat OUD with FDA-approved medications, including buprenorphine, in treatment settings other than OTPs.
- The Comprehensive Addiction and Recovery Act of 2016 (CARA), signed into law in 2016, endorses the use of MOUD for OUD and amends the CSA to, under certain conditions and restrictions, raise the total number of patients to which the prescriber can dispense buprenorphine from 30 to 100 per year.
- The SUPPORT for Patients and Communities Act of 2018 extends the privilege of prescribing buprenorphine in office-based settings to qualifying nurse practitioners, physician assistants, clinical nurse specialists, certified registered nurse anesthetists, and certified nurse-midwifes until October 1, 2023. HCPs may treat up to 100 patients in the first year of the waiver if the physician is board certified in addiction medicine or addiction psychiatry or the clinic is a "qualified practice setting."

A qualified practice setting under the SUPPORT ACT meets the following conditions:[188]

- Provides professional coverage for patient medical emergencies during hours the practice is closed
- Provides access to case-management services (e.g., medical, behavioral, social, housing, employment, educational, other)
- Uses health information technology systems such as electronic health records
- Is registered for the state PDMP
- Accepts third-party payment for health services

After one year at the 100-patient limit, qualifying practitioners who meet the above criteria can apply to increase their patient limit to 275. Certain qualifying practitioners may treat OUD with MOUD without a buprenorphine waiver under special circumstances that include medical emergencies and are detailed as follows: https://www.samhsa.gov/medication-assisted-treatment/statutes-regulations-guidelines/special-circumstances.

Guidance for state medical boards and HCPs in office-based OUD treatment is available. The FSMB Model Policy on DATA 2000 and Treatment of Opioid Addiction in the Medical Office may be downloaded from the following link: http://legalsideofpain.com/uploads/FSMB-2013_model_policy_treatment_opioid_addiction.pdf.

Diversion

Diversion of CS a significant public health problem that contributes to harm in the form of increased fatal and nonfatal overdoses, criminal activity, ED visits, and SUD development. The economic burden of opioid misuse reaches $78.5 billion a year in healthcare, lost productivity, addiction treatment, and criminal justice costs.[189] Diversion occurs any time a prescribed, controlled medication is deflected from its intended medical source to an unintended purpose and can occur at any point along the supply chain. Common types of diversion are shown in Table 8.[42] Diversion and misuse create a loop that leads to more overdoses deaths and widespread development of SUDs.[18]

Most misused opioids are obtained through diversion. Year after year, the National Survey on Drug Use and Health, conducted annually by SAMHSA, reports that most people who misuse prescription opioids either bought them, were given them, or took them without asking from family members or friends.[190] About a third of people who misuse opioids get them by prescription from one doctor.[190]

Leftover pills from acute pain prescriptions are a chief source of diverted and misused opioids. One systematic review found that 42% to 71% of opioids obtained by surgical patients went unused.[191] Leftover CS in medicine cabinets can then become a significant source for diversion.

The American College of Emergency Physicians has identified acute low back pain and exacerbations of chronic pain as common presenting complaints in the ED. When patients present to an ED with these common complaints, the ACEP recommends that the HCP assess whether non-opioid therapies would be adequate pain treatment and reserve opioids for severe pain that would be unresponsive to other therapies.[168]

Patients should be counseled never to share opioids or other CS with any other person and to store opioids in a locked area away from other family members and visitors.[38] Leftover opioids, including transdermal fentanyl patches, should not be placed in the trash but should be taken to an authorized drug take-back facility or, if one is not available, flushed down the toilet or washed down the drain immediately.[192] More information about drug disposal and national drug take-back events is available by calling 1-800-882-9539 or visiting the website (https://www.deadiversion.usdoj.gov/drug_disposal/index.html) of the Drug Enforcement Administration. The FDA maintains a "flush list" of opioid and non-opioid drugs that should be disposed of promptly if no take-back option is available: https://www.fda.gov/drugs/disposal-unused-medicines-what-you-should-know/drug-disposal-fdas-flush-list-certain-medicines.

Certain medications are highly sought for diversion as identified by the DEA and NIDA and shown in Table 9.[42] Some prescription drugs sell on the street for as much as $50 a pill and, unfortunately, some patients sell the drugs prescribed to them as a way of earning money to pay expenses or to finance their desire to buy street drugs.[18] To be clear, most patients who take opioids for pain do not misuse or divert their pills.[190] However, HCPs should understand that some people who visit a medical facility for pain are actually seeking opioids to divert or misuse and take relevant precautions to prevent diversion as required by the DEA. Some patients may have the disease of OUD and should be managed accordingly.

Distinguishing would-be diverters from patients is difficult at best. Although no behavior reliably indicates drug diversion, the chances of detecting such deception increase when HCPs watch for patterns of behavior.

Table 8. Common Types of Drug Diversion	
Method	**Definition**
Selling Prescription Drugs	Patients and non-patients sell prescription drugs that were obtained illegally
"Doctor Shopping"	Soliciting multiple prescribers under false pretenses to obtain CS prescriptions
Illegal Internet Pharmacies	Rogue websites under the guise of legitimate pharmacies provide CS to people without prescriptions, evading state licensing requirements, operating across state and international borders
Theft	May occur at any step of the supply chain (examples: manufacturers, patients, patient's relatives or friends, HCPs, pharmacists)
Prescription Pad Theft and Forgery	Printing or stealing prescription pads to write fraudulent prescriptions, altering existing prescriptions to obtain unauthorized quantity

Table 9. Drugs with Highest Potential for Diversion and Misuse	
Drug Class	**Examples**
Anabolic Steroids	Methyltestosterone Testosterone
Depressants	Barbiturates: pentobarbital Benzodiazepines: alprazolam, diazepam
Hallucinogens	Ketamine
Opioids	Diphenoxylate Fentanyl Hydrocodone Hydromorphone Meperidine Methadone Morphine Oxycodone Oxymorphone
Stimulants	Amphetamine Dextroamphetamine Methamphetamine Methylphenidate
Centers for Medicare and Medicaid Services. Partners in Integrity: What is a Prescriber's Role in Preventing the Diversion of Prescription Drugs? https://www.pharmacy.umn.edu/sites/pharmacy.umn.edu/files/prescriber_role_in_preventing_diversion.pdf Accessed Sep 17, 2021.	

The DEA has listed some common behaviors that should not be considered an exhaustive list but that might indicate a person seen in-clinic is seeking drugs to divert or misuse:[26]

- Demanding to be seen immediately
- Stating that they are visiting the area and need a prescription to tide them over until seeing a local HCP
- Appearing to feign symptoms, such as abdominal or back pain or pain from kidney stones or a migraine in an effort to obtain opioids
- Claiming non-opioid analgesics do not work
- Requesting a particular opioid
- Complaining that a prescription has been lost or stolen and needs replacing
- Requesting more refills than originally prescribed
- Using pressure tactics or threatening behavior to obtain a prescription
- Showing visible signs of drug abuse, such as track marks

Clinical practices to minimize the potential diversion when seeing patients include:[42]

- Caution when prescribing to patients who request combinations of drugs that may enhance effects, such as opioids with benzodiazepines
- Thorough documentation when prescribing or choosing not to prescribe opioids
- Keeping a DEA registrant or license number confidential unless disclosure is required
- Protecting access to prescription pads
- Ensuring that prescriptions are written clearly to minimize the potential for forgery
- Moving to electronic prescribing so that paper prescriptions are not required
- Adhering to strict refill policies and educating office staff
- Using PDMPs in accordance with state regulation and expert guidance
- Referring patients with extensive pain management or prescription needs to specialists in relevant fields
- Collaborating with pharmacists and other providers to verify prescription authenticity and medical necessity
- Collaborating with pharmacy benefit managers and managed care plans that seek to determine medical necessity of prescriptions

HCPs often have the first opportunity to prevent, identify, and report CS diversion. If diversion has occurred, the following agencies should be notified:

- Local law enforcement and local fraud alert networks
- DEA: https://www.deadiversion.usdoj.gov/webforms/dtlLogin.jsp
- HHS Office of Inspector General National Hotline: 1-800-HHS-TIPS (1-800-447-8477) or TTY 1-800-377-4950
- For information on fraud prevention and detection compliance guidance, visit http://www.oig.hhs.gov/

Prescription drugs are also diverted by HCPs in various health care settings.[193] Medical professionals engage in diversion for myriad reasons that include recreation, an active SUD, financial gain, self-medication for pain or sleep, or to manage withdrawal symptoms.[42]

Mismanagement of patients by HCPs can also happen because the HCPs were duped into believing claims of pain were legitimate, because their practice ideas are dated, or because they are themselves dishonest and are aware their patients are diverting. Financial gain can motivate fraud on the part of a prescriber. For example, in August 2010, a New York physician was charged with leading a drug ring that allegedly provided oxycodone prescriptions to patients with no medical need, arranged to resell the drug to third parties, and distributed more than 11,000 pills resulting in a $1 million expense to the Medicaid program.[42]

Certain signs should alert supervisors to the possibility that diversion may be occurring, for example:[194]

- Removing CS without a doctor's order
- Removing CS for patients "not assigned" to them
- Removing CS for patients that have been discharged
- Removing CS and not documenting them
- Pulling excessive quantities of as-needed medication compared to other health care workers assigned to the patient
- Exhibiting discrepancies in inventory on a regular basis
- Pulling out CS in lower dosages in order to obtain more pills when the exact dosage is available
- Removing as-needed medications too frequently, for example pulling every 2 hours when the order is for every 4 hours
- Pulling out larger dosages of injectable medications to obtain more waste
- Experiencing continuing patient complaints of pain, despite documented administration of pain medications
- Falsifying records and failing to document waste

Staff members who are engaging in diversion within a facility such as a hospital may often volunteer to witness or administer CS, have major life changes or injuries, frequently disappear from the floor, or have periods of high and low productivity not consistent with colleagues.

Staff members other than HCPs may also divert medications. Support staff employees who may be diverting CS may be spotted in areas where they are not unauthorized, may unnecessarily touch syringes, may stay late when their services are unnecessary, and may always volunteer to help dispose of waste.[194] If either HCPs or support staff are impaired, they may appear sleepy, exhibit personality changes, commit multiple errors or be unable to perform routine tasks, take excessive sick leave or extended breaks, and be the target of multiple patient complaints.[194]

The best way to prevent diversion within an institution is to set a clear diversion prevention plan.[193] The following are some strategies that do not comprise an exhaustive list:

- Account for every dosage form from order to administration
- Utilize a CS management system within an integrated platform
- Document waste within electronic system
- Link CS administration record to patient electronic health record (also medication returns)
- Segregate duties so that no one can carry out and conceal an activity within daily responsibilities
- Limit access to the CS ordering system
- Ensure no one is immune from oversight and separation
- Conduct periodic reviews of responsibility

To effectively combat diversion, cooperation is necessary across multiple teams and facility divisions. The Mayo Clinic has laid out the following set of recommended steps when diversion in the workplace is suspected or identified:[193]

- Secure whatever evidence is available
- Initiate drug testing
- Initiate a discussion with the employee's supervisor
- Review of any records documenting handling of CS
- Institute additional surveillance if necessary
- Initiate recurring meetings of a drug diversion response team to review findings
- Quickly remove from patient care any employee found to have diverted CS
- Quickly close the case of any employee determined not to have diverted CS
- Report findings to the DEA, the state pharmacy board, and local law enforcement

More possibilities include urine drug screening and agreement to comply with diversion prevention policies prior to hiring in addition to ongoing random or "for cause" testing. Newly hired facility workers should receive education to prevent diversion, and that education should be ongoing. Mandatory reporting procedures and methods of surveillance, including checks of prescribing records and video surveillance, should be in place. It is important to check relevant laws in the state of practice as some states require that diversion of CS be reported to federal authorities and result in loss of license to practice medicine.

After taking some time to absorb the signs of diversion within a healthcare facility, read over the case example that follows and consider what steps should be taken.

BEFORE MOVING ONTO THE NEXT SECTION, PLEASE COMPLETE CASE STUDY 4 ON THE NEXT PAGE.

Conclusions

This activity summarizes the regulatory framework and clinical recommendations necessary to prescribe CS safely. Knowledge of best practices must be accompanied by clinical implementation to ensure appropriate treatment of patients commonly treated with CS for a variety of medical indications. Key precautions in prescribing CS include selecting appropriate candidates on the basis of their medical condition and degree of risk, following evidence-based protocols for treatment, and recognizing problematic or dangerous use patterns that call for intervention. This includes recognizing the value of evidence-based medications for OUD.

It is imperative that HCPs keep current with changing federal, state, and local requirements, to prescribe the lowest effective doses of CS used with a variety of medical conditions, to monitor patients for any ill effects, and to help safeguard society from the dangers brought by the misuse and diversion of these powerful drugs.

Case Study 4

Instructions: Spend 5-10 minutes reviewing the case below and considering the questions that follow.

Georgia is an intensive care unit nurse with twenty years' experience in caring for critically injured patients. She is training Moshe, a new nurse fresh from graduate school. One day, as he is returning from lunch, he sees Georgia leaving the room of one of his patients. This pattern repeats over the course of the next month. On one of these occasions, he questions Georgia as to the patient's condition. Georgia replies that the patient was in pain and needed a bolus dose of fentanyl.

The next day, when Moshe sees Georgia leaving his patient's room, he inspects the fentanyl drip and sees that it has more volume than when he left on break earlier. He further learns that patients on fentanyl drips on this floor have been showing signs of inadequate analgesia. Subsequent investigation shows that the fentanyl drips have been diluted.

1. **What is Moshe's responsibility in this scenario?** _____

2. **How might the management of the facility respond?** _____

3. **What steps might be taken to safeguard the integrity of patient treatment?** _____

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Self-Assessment

Choose the best possible answer for each question and mark your answers on the self-assessment answer sheet at the end of this book. There is a required score of 70% or better to receive a certificate of completion.

11. Under the Controlled Substances Act, the federal government considers cannabis:

A. To have the highest risk for substance-use disorder and no accepted medical uses.
B. To have the highest risk for substance-use disorder and limited medical uses.
C. To have a low risk for substance-use disorder and no accepted medical uses.
D. To have medical uses that are left to the discretion of individual states.

12. The Drug Enforcement Administration has named recurring patterns that might indicate inappropriate controlled substances (CS) prescribing, including which of the following?

A. No logical relationship between prescribed drugs and alleged medical condition.
B. More than 70 patients scheduled per day.
C. Evidence that prescribers have not completed required continuing medical education.
D. Failure to use evidence-based patient evaluation tools for addiction.

13. Attention deficit hyperactivity disorder is characterized by:

A. Persistent pattern of inattention that also must include impulsivity.
B. Symptoms present for at least 9 months.
C. Evidence of cognitive delay.
D. Symptoms that are developmentally inappropriate.

14. Optimal treatment for narcolepsy:

A. Combines CS and non-CS medications.
B. Is not recommended in pediatric patients.
C. Is risky in patients older than 65 years.
D. Should incorporate non-medication components.

15. A common instruction to the patient contained in a treatment agreement for provision of opioids (or another CS) is:

A. To promise to report misuse of CS by family members.
B. To discontinue use of any previously prescribed CS.
C. To safeguard CS medications from others and dispose of properly.
D. To produce written records of any previous drug-related arrests.

16. Patients with OUD or other problems managing opioids who are tapered or suddenly discontinued from opioids non-collaboratively are at risk for:

A. Gastrointestinal complications.
B. Suicidal ideation.
C. Serious drug-drug interactions with remaining CS in regimen.
D. Development of neuropathic pain.

17. Which medication should be withdrawn slowly over months when taper is indicated to prevent the possibility of hallucinations?

A. Hydrocodone.
B. Methylphenidate.
C. Trazodone.
D. Diazepam.

18. The following FDA-approved medications to treat OUD are:

A. Methadone and naltrexone.
B. Buprenorphine and naltrexone.
C. Methadone and buprenorphine.
D. Buprenorphine-naloxone combination and cannabidiol.

19. Of the following choices, which drug has been identified by the Drug Enforcement Administration and the National Institute on Drug Abuse as having the highest potential for diversion?

A. Ketamine.
B. Cyclobenzaprine.
C. Carisoprodol.
D. Gabapentin.

20. Which of the following is a measure to be enacted at a healthcare facility when diversion of CS by a healthcare worker is discovered?

A. Institute an in-house criminal background check of the employee found to have diverted CS.
B. Quickly remove from patient care any employee found to have diverted CS.
C. Call an immediate meeting to report findings to all staff and support employees.
D. Report findings to local media.

NOTES

EXISTING AND EMERGING PATIENT SAFETY PRACTICES

COURSE DATES:	MAXIMUM CREDITS:	FORMAT:
Release Date: 1/2022 Exp. Date: 12/2024	*12 AMA PRA Category 1 Credits*™	Enduring Material (Self Study)

TARGET AUDIENCE

This course is designed for all physicians (MD/DO) and other health care practitioners.

HOW TO RECEIVE CREDIT:

- Read the course materials.
- Complete the self-assessment questions at the end. A score of 70% is required.
- Return your customer information/ answer sheet, evaluation, and payment to InforMed by mail, phone, fax or complete online at program website.

COURSE OBJECTIVE

The purpose of this course is to summarize a range of issues related to patient safety practices (PSPs) that are relevant to practicing clinicians and seeks to support a culture of safety across the healthcare continuum. Topics include issues such as addressing the opioid crisis and emerging health risks (e.g., multidrug-resistant organisms) and overall directives to "put patients first" and to reduce provider burden and burnout.

LEARNING OBJECTIVES

Completion of this course will better enable the course participant to:

1. Understand the roles that clinical decision support, result notification systems, and education and training play in helping to reduce diagnostic errors.
2. Describe the potential hazards of alarm fatigue and be able to describe at least three strategies for reducing this risk.
3. Understand how antimicrobial stewardship can help reduce the risk of *C. difficile* transmission and infection.
4. Describe at least three strategies to reduce the rate of adverse events in older adults.

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STAFF AND CONTENT REVIEWERS

InforMed staff, input committee and all content validation reviewers involved with this activity have reported no relevant financial relationships with commercial interests.

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DISCLAIMER

Introduction

Every year, millions of patients suffer injuries or die because of unsafe or poor-quality health care. Many medical practices and risks associated with health care pose major challenges for patient safety and contribute significantly to the burden of harm due to unsafe care. Improving patient safety involves every level of care, from individual practitioners to practice-based systems of operation and all the way up to the highest levels of health care policy reforms.

This learning activity summarizes a range of issues related to patient safety practices (PSPs) that are relevant to practicing clinicians. The activity is based on The Making Health Care Safer report from the Agency for Healthcare Research and Quality (AHRQ). Previous AHRQ reports have helped to reduce harm and improve the safety and quality of care for patients. The reports analyze the evidence for various patient safety practices and have also identified contextual factors that contribute to successful PSP implementation. The reports have helped to shape national discussion regarding patient safety issues on which providers, payers, policymakers, and patients and families should focus.

This activity seeks to support a culture of safety across the healthcare continuum, including in nursing homes, home care, outpatient, and ambulatory settings, and during care transitions. The scope of this activity is intentionally broad and includes issues such as addressing the opioid crisis and emerging health risks (e.g., multidrug-resistant organisms) and overall directives to "put patients first" and to reduce provider burden and burnout.

Patient safety practices are discrete and clearly-recognizable structures or processes used for the provision of care that are intended to reduce the likelihood and/or severity of harm due to systems, processes, or environments of care. A PSP may have varying degrees of evidence to support its ability to prevent or mitigate harm. This activity focuses on PSPs chosen for the high-impact harms they address and include diagnostic errors, failure to rescue, infections, and nursing-sensitive conditions.

The most significant harms patients face continue to be found in higher acuity settings, such as the emergency department and ICU. One "setting" that poses a unique threat to patients is the transition between one setting and another: the hospital to the outpatient setting, in particular.

Several broad themes will emerge from this learning activity:

- More than one PSP can be used to reduce a given harm.
- The context in which a PSP is implemented determines success.
- Selecting a particular PSP should be based on the root cause of the harm. If a facility is experiencing an increase in sepsis mortality, the root cause may be a lack of recognition of patients with sepsis arriving to the ED. In another facility, it may be due to lack of monitoring of patients who are experiencing deterioration on a medical-surgical unit.
- When using a specific PSP, consideration must be given to potential new harms that can be introduced. For example, strategies to improve anticoagulation-related events must be balanced with strategies used to reduce venous thromboembolism.
- PSPs are not implemented in isolation and are often part of a broader safety strategy. The strategy often relies on a strong safety culture, teamwork, communication, and involvement of the patient and family. These cross-cutting practices are the foundation for success.

Diagnostic Errors

Diagnostic error is an increasingly-recognized threat to public health, with estimates of 5% of adults being affected in the outpatient environment.[1] In the hospital setting, diagnostic error is responsible for 6% to 17% of adverse events.[2] Diagnostic error has also been shown to be responsible for more closed malpractice claims than other causes.[3] The Institute of Medicine (now the National Academy of Sciences), in its seminal report on diagnostic safety, concluded that "most people will experience at least one diagnostic error in their lifetime."[4]

A diagnostic error is "the failure to (a) establish an accurate and timely explanation of the patient's health problem(s) or (b) communicate that explanation to the patient."[1] This definition focuses on the outcomes of the diagnostic process, recognizing that diagnosis is an iterative process that solidifies as more information becomes available. The diagnosis needs to be timely and accurate so that appropriate treatment is initiated to optimize the patient's outcome. Any gaps that arise in the diagnostic process can lead to error.

This chapter reviews four patient safety practices that have the potential to decrease diagnostic errors: the use of clinical decision support (CDS); result notification systems (RNS); education and training; and peer review.

- **CDS** offers solutions integrated into the workflow to address diagnostic errors by providing stakeholders with knowledge and person-specific information, intelligently filtered or presented at appropriate times, to improve decision making and communication.
- **RNSs** aim to address lapses in communication, a contributing factor to delayed diagnosis and treatment of patients in both ambulatory and inpatient settings.
- **Education and training** on the diagnostic process enhance clinical reasoning and decrease biases.
- **Peer review** identifies potential diagnostic errors before they reach the patient and provides feedback with the intent of improving clinical practice and quality.

Clinical Decision Support

Diagnostic error is a complex and multifaceted problem that requires systems solutions to achieve the necessary changes. Advancements in health information technology (IT) represent thoughtful and sophisticated ways to reduce delayed, missed, or incorrect diagnoses. Contributions of health IT include more meaningful incorporation of evidence-based diagnostic protocols with clinical workflow, and better usability and interfaces in the electronic health record (EHR).

CDS provides clinicians, staff, patients or other individuals with knowledge and person-specific information, intelligently filtered or presented at appropriate times, to enhance health and healthcare. CDS encompasses a variety of tools to enhance decision making in the clinical workflow. These tools include computerized alerts and reminders to care providers and patients; clinical guidelines; condition-specific order sets; focused patient data reports and summaries; documentation templates; diagnostic support, and contextually relevant reference information, among other tools.

CDS represents a range of different interventions, from documentation templates to popup alerts. The knowledge bases triggering CDS differ as well. Rules-based or logic-based CDS often takes the form of IF-THEN rules. More advanced CDS leveraging artificial intelligence (AI) and machine learning taps awareness of past experiences and patterns in clinical data. These techniques have generated interest in their potential to better augment clinician intelligence and support decision making.

Several patient safety researchers have suggested that health IT, including CDS, can be leveraged to improve diagnosis, although the data have been mixed. An example of a CDS are differential diagnosis (DDX) generators. DDX generators are programs that assist healthcare professionals in clinical decision making by generating a differential diagnosis based on a minimum of two items of patient data. DDX generators provide a list of potential diagnoses for consideration, sometimes in order of likelihood based on available information, as a means to improve diagnosis.

Several investigational CDS tools exist to assist with diagnostic study interpretation, including imaging studies, electrocardiograms (ECGs), and pathology. Although these CDS tools are proof-of-concept in nature, they demonstrate the potential to augment clinician diagnostic performance but not completely replace it.

Use in Imaging

Three papers have evaluated techniques to assist with interpretation of imaging studies. All were investigational in nature, describing the development and validation of the models. Herweh et al. (2016) compared the diagnostic performance of an automated machine-learning algorithm to detect acute stroke on CT scans using a standardized scoring method to the performance of stroke experts and novices using the algorithm.[5] Although this study had a small sample size, the automated tool showed similar scoring results to that of experts and better performance than the novices.

Bien et al. (2018) used deep learning, a subset of machine learning, to model the complex relationships between images and their interpretations.[6] The model was designed to detect general abnormalities and two specific diagnoses (anterior cruciate ligament tears and meniscal tears) on knee magnetic resonance imaging. For general abnormalities, there was no difference between the performance of the model and the general radiologists. For ACL tear detection, the model was highly specific but not significantly different from the specificity achieved by the radiologists. The authors also found that providing the radiologists with the predictions from the model improved their quality of interpretation of the MRI studies.

Li et al. (2018) developed an AI tool to detect nasopharyngeal malignancies under endoscopic evaluation by oncologists.[7] Results indicate that the tool was significantly better in its performance compared with oncological experts; the overall accuracy was 88% vs. 80.5%.

ECG Interpretation

In the evaluation of cardiac health, 12-lead ECGs are accompanied by computer interpretations to assist the clinician with diagnoses. These interpretations have been shown to often be inaccurate, primarily because of noisy background signals that interfere with automated pattern recognition by the machine algorithms. However, four studies evaluated ECG interpretations by automated systems, and all found that the systems were no better or worse than human performance alone.

Use in Pathology

Two studies evaluated the use of AI to aid in the diagnostic work of pathologists. Vandenberghe et al. (2017) developed and evaluated the use of deep learning, an AI method, to identify specific cancer cell types.[8] For 71 breast tumor samples, they found that the use of this computer-aided diagnosis tool had a concordance rate of 83% with pathologist review. The pathologist re-reviewed the 12 samples that had discordance between the diagnoses of the pathologist and the computer-aided diagnosis tool, prompting modifications to 8 of the original diagnoses.

Xiong et al. (2018), also using deep learning, developed and tested an AI-assisted method for the automatic detection of mycobacterium tuberculosis.[9] Results showed high sensitivity (97.9%) and moderate specificity (83.6%), with 2 false negatives and 17 false positive cases due to contaminants.

Potential Benefits and Barriers

In general, CDS tools have an added benefit of improving access to specialized care by providing theclinician with assistance in diagnosing conditions that would typically fall in the realm of a specialist. Several CDS tools, in addition to improving diagnostic accuracy, would also allow prioritization of work, creating greater efficiencies and improving workflow once implemented in clinical settings. These systems flagged studies or diagnoses that required follow-up, allowing the clinicians to prioritize their work. For the CDS tools that generate DDX, some have raised the concern that presenting the clinician with a long list of diagnostic possibilities could be distracting or lead to unnecessary testing and procedures.

The information generated by CDS for use in diagnosis is only as good as the information that is put into the system. For example, if the clinician interprets the physical exam incorrectly (e.g., saying that a physical sign is absent when it is present) and inputs that incorrect information into the tool, that error may negatively affect any diagnosis that is partially based on the presence of that sign. Accurate diagnosis can be achieved only if the clinician's assessment of the patients' signs and symptoms is correct, because the automated system will process only data that humans introduce.

In the case of ECG interpretation, accurate ECG recording depends on many variables, including lead placement, weight, movement, coexisting electrolyte abnormalities, and symptoms. If the placement is wrong (e.g., leads are placed in wrong location), the interpretation may be wrong.

Leveraging the "CDS Five Rights" Approach

A useful framework for achieving success in CDS design, development, and implementation is the "CDS Five Rights" approach.[10] This model states that CDS-supported improvements in desired healthcare outcomes can be achieved if clinicians communicate:

1. The right information: evidence-based, suitable to guide action, pertinent to the circumstance
2. To the right person: considering all members of the care team, including clinicians, patients, and their caretakers
3. In the right CDS intervention format, such as an alert, order set, or reference information to answer a clinical question
4. Through the right channel: for example, a clinical information system such as the EHR, a personal health record, or a more general channel such as the Internet or a mobile device
5. At the right time in workflow, for example, at the time of decision/action/need.

CDS has not reached its full potential in driving care transformation, in part because opportunities to optimize each of the five rights have not been fully explored and cultivated.

Providing the Right Information to the End User: The process of integrating real-time analytics into clinical workflow represents a shift towards more agile and collaborative infrastructure building, expected to be a key feature of future health information technology strategies. As interoperability and big data analytics capabilities become increasingly central to crafting the healthcare information systems of the future, the need to address issues that ease the flow of health information and communication becomes even more important.

Without tools that select, aggregate, and visualize relevant information among the vast display of information competing for visual processing, clinicians must rely on cues by "hunting and gathering" in the EHR. Alerts that embody "right information" should provide just enough data to drive end user action, but not so much as to cause overload. Overload can create alert fatigue and lead to desensitization to the alerts, resulting in the failure to respond to warnings, both important and less important. Experience from the use of CDS in the medication ordering process has demonstrated this paradoxical increase in risk of harm due to alerts that were intended to improve safety.

Providing Information in the Right Format: Lack of knowledge regarding how to present CDS to providers has impeded alert optimization, specifically the most effective ways to differentiate alerts, highlighting important pieces of information without adding noise, to create a universal standard. Thepotential solution that CDS represents is limited by problems associated with improper design, implementation, and local customization. In the absence of evidence-based guidelines specific to EHR alerting, effective alert design can be informed by several guidelines for design, implementation, and reengineering that help providers take the correct action at the correct time in response to recognitionof the patient's condition.

Right Workflow: A well-thought-out user-centered design or equivalent process during the implementation phase includes critical elements of leadership buy-in, dissemination plans, and outcome measurements. Knowledge needs to be gained about how to implement the CDS and how to create an interface between the system and the clinician that takes into consideration the cognitive and clinical workflow. The optimal approach to CDS should not be focused primarily—or even secondarily—on technology. Implementation is about people, processes, and technology. Systems engineering approaches, including consideration of user experience and improvements in user interface, can greatly improve the ability of CDS tools to reach their potential to improve quality of care and patient outcomes. The application of human factors engineering in determining the right workflow includes but is not limited to ethnographic research including workflow analysis and usability testing.

Measurement

Successful CDS deployment requires evaluating not only whether the intended clinicians are using the tool at the point of care, but also whether CDS use translates into improvements in clinical outcomes, workflows, and provider and patient satisfaction. However, success measures are often not clearly enunciated at the outset when developing or implementing CDS tools. As a result, it is often difficult to quantify the extent to which CDS has been effectively deployed, as well as whether it is effective at managing the original diagnostic problem it was designed to address.

Result notification systems

Failure to communicate test results has been repeatedly noted as a contributing factor to delayed diagnosis and treatment of patients in both ambulatory and inpatient settings. Due to the negative impact on patients of missed communication of results, The Joint Commission made timely reporting of critical results of tests and diagnostic procedures a National Patient Safety Goal for their Critical Access Hospital and Hospital Programs.[11]

The laboratory and radiographic testing process has three distinct phases: the pre-analytic phase, during which the test is ordered and that order is implemented; the analytic phase, when the test is performed; and the post-analytic phase, in which results are relayed to the ordering clinician, who acts upon the results, and notifies and follows up with the patient (Figure 1).

The post-analytic phase, specifically the step where results, clinically significant test results (CSTR) in particular, are relayed back to the ordering clinician, is a source of diagnostic error. To reduce errors that occur during this step, experts have advocated for the use of automated alert notification systemsto ensure timely communication of CSTR. Result notification systems (RNS) can be completely automated, where an abnormal result generates an alert to the ordering clinician; or the RNS may require manual activation by the clinician. There are also a variety of modalities that can be used to alert the practitioner of actionable test results, including short messages relayed via mobile phones; emails; and results (with or without accompanying alerts) in the EHR.

Some have raised a hypothetical concern about alert fatigue, a potential unintended consequence of implementing alerting RNSs. Etchells et al. (2010) noted that critical results, such as those from repeated troponin tests, were viewed as nuisances by receiving clinicians during a pilot of the system.[12] They also noted that because physician schedules were not fully automated, it was not possible to consistently route critical results to a responsible and available physician to take action. To compensate for this, physicians handed off "critical value pagers" so that the physician-on-call carried several pagers. Although this could reduce the number of missed alerts, it also created confusion when the on-call physician often could not discern which pager was alerting.

Dalal et al. (2014) attributed the successful implementation of their TPAD email-generating RNS to the existing institutional culture that supports the use of email as a routine part of clinical care.[13] The RNS was integrated into their current practice, which facilitated uptake. Several authors mentioned the need for clear policies and procedures for the RNS such as the need to have clear policies about who is responsible for acknowledging an alert and taking action, so that there is no ambiguity. One institution, after much deliberation, established the policy that the responsibility for following up a test rested on the "ordering" clinician, and that this responsibility could be discharged only after a handoff where the "new owner" recipient acknowledged receipt and agreed to take over the follow-up.

Automated physician scheduling is important for optimal performance of automated critical value alerting systems. For example, when physician schedules are not fully automated, it is impossible to route alerts to the responsible (e.g., on-call) physician who can take action.

Although studies of this topic are generally of high quality and some findings are significant, studies in other settings are needed to test and demonstrate generalizability, as well as to engage research in this field more widely. Diagnostic errors due to lapses in communication occur during care transitions, but only three studies (all in the same healthcare system) evaluated RNS to improve delivery of results finalized after the transition from the inpatient to the outpatient setting. It is challenging when many providers are taking care of a patient, as the RNS needs to discern who is responsible for which patient at any given time. Institutions are establishing policies aimed at addressing this challenge, but how the policies perform needs to be investigated.

Education and training

In the 2015 National Academies of Sciences, Engineering, and Medicine (NASEM) report Improving Diagnosis in Health Care, one of the recommended strategies for improving diagnosis is to enhance healthcare professional education and training in the diagnostic process.[4] The content of this education can be guided by an understanding of the root causes of diagnostic errors. Studies have uncovered two broad categories of underlying root causes: cognitive-based factors, such as failed heuristics; and systems-based factors, such as lack of provider-to-provider communication and coordination. In the realm of cognitive-based errors, there are also two main streams of thought about causes: heuristics failures and shortcomings in disease-specific knowledge and experience. These sets of broad conceptual factors are by no means mutually exclusive, and ideally system redesign and educational efforts can leverage overlaps and synergies. How to best provide education and training to change these underlying factors and thereby improve diagnostic accuracy and reduce diagnostic errors leads to a more fundamental question of whether education and training lead to improved diagnostic performance.

General training in clinical reasoning

Clinical reasoning is the process by which clinicians collect data, process the information, and develop a problem representation, leading to the generation and testing of a hypothesis to eventually arrive at adiagnosis.

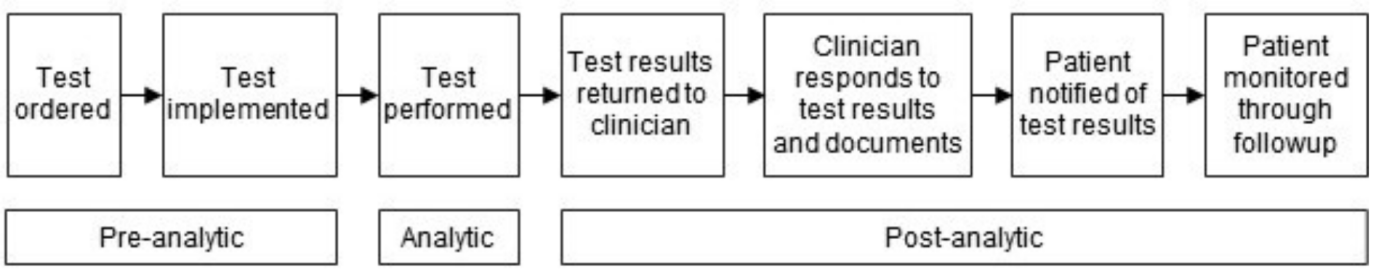
Cook et al. (2010) conducted a meta-analysis and systematic review of the effects on training outcomes of using virtual patients, including the effects on clinical reasoning.[14] The learners interact with a computer program that simulates real-life clinical scenarios to obtain a history, conduct a physical exam, and make diagnostic and treatment decisions. The main takeaway from this meta-analysis and review was that the use of virtual patients is associated with large positive effects on clinical reasoning and other learning outcomes when compared with no intervention and is associated with small effects in comparison with noncomputer instruction.

BEFORE MOVING ONTO THE NEXT SECTION, PLEASE COMPLETE CASE STUDY 1 ON THE NEXT PAGE.

Training in metacognitive skills to reduce biases

Cognitive biases can affect clinical reasoning and influence the diagnostic process, contributing to a large proportion of misdiagnoses. Metacognition, the understanding, control, and monitoring of one's cognitive processes, can be used to gain better insight and counteract these biases. A review of studies focused on techniques to enhance metacognitive skills found mixed results, but overall they suggest the use of training metacognitive strategies to improve diagnostic performance.

Figure 1: Conceptual Framework of the Testing Process



Case Study 1: Teaching Clinical Reasoning

Instructions: Spend 10 minutes reviewing the case below and considering the questions that follow.

The main goals of clinical teaching include assessing students' clinical reasoning skills, facilitating and strengthening their development, and providing them with opportunities for practice and feedback. These goals have important implications for learning because the quality of the clinical reasoning strategies that medical students use influences diagnostic success.

In 2004 clinicians at Case Western Reserve University School of Medicine decided to test the effectiveness of a technique that promised time-efficient teaching methods in the clinical setting that provide insights into the students' clinical reasoning strategies and uncertainties while also allowing the preceptor to remain fully engaged in the priorities of patient care.[15]

The SNAPPS technique is a learner-centered case presentation technique that depends mostly on the student for its successful implementation. The six-step mnemonic outlines a collaborative case presentation that the student leads and the preceptor facilitates. A concise summary of the facts is followed by five steps that facilitate the expression of diagnostic reasoning and case-related uncertainties. SNAPPS is intended to redirect, but not lengthen, the learning encounter by condensing the reporting of facts and encouraging the expression of reasoning and uncertainties. Brief faculty development coupled with more extensive learner development serve as companion pieces in the successful implementation of this learner-driven technique:

***Summarize** briefly the history and findings.*
***Narrow** the differential to two or three relevant possibilities.*
***Analyze** the differential by comparing and contrasting the possibilities.*
***Probe** the preceptor by asking questions about uncertainties, difficulties, or alternative approaches.*
***Plan** management for the patient's medical issues.*
***Select** a case-related issue for self-study.*

Sixty-four third-year medical students were randomly assigned to three groups: SNAPPS, feedback training, and usual-and-customary instruction. Although the authors did not assess whether the differential diagnoses were accurate, they found that students using the SNAPPS technique performed better on all outcomes, including analyzing possibilities of the differential diagnosis, expressing uncertainties, and obtaining clarification. "SNAPPS greatly facilitates and enhances expression of diagnostic reasoning and uncertainties during case presentations to ambulatory care preceptors," the authors reported. "Students can conduct case presentations using a technique that makes each step explicit and gives learners, rather than preceptors, the responsibility for expressing their clinical reasoning and uncertainties."

1. **Thinking about your own institution or your own training, how effective do you think teaching about clinical reasoning skills is (or was)? In what ways could that teaching be improved?**_____

2. **Do you think the steps in the SNAPPS approach are realistic in modern teaching hospitals? Why or why not?**_____

3. **What do you think is the single most important skill medical students and practicing clinicians need to develop to improve decision-making abilities and reduce diagnostic errors?**_____

A study by Smith and Slack (2015) of family medicine residents who participated in a debiasing workshop found that the residents' ability to formulate an acceptable plan to mitigate the effect of cognitive biases significantly improved after the training ($p=0.02$), although the residents were not able to translate the plan into practice, as evidenced by no change in the outcomes of preceptor concurrence with the residents' diagnoses, residents' ability to recognize their risk of bias, and the preceptors' perception of an unrecognized bias in the residents' presentations.[16] Novice diagnosticians, such as medical students, may lack sufficient experience to employ nonanalytic reasoning, rendering these methods increasingly more useful as experience increases.

Training on the use of heuristics

Heuristics are decision strategies, or mental shortcuts, that allow fast processing of information to arrive at a decision or judgment. One type of heuristic is representativeness; the use of the degree to which an event is representative of other, similar events to assess the probability of an event occurring. Although the literature around the use of heuristics in medicine tends to focus on the biases they introduce, there is a recognized potential for training with heuristics to achieve better diagnostic accuracy.

Mohan et al. (2018) conducted a randomized controlled trial comparing two training interventions designed to improve the use of the representativeness heuristic to improve trauma triage by emergency physicians.[17] The authors developed two serious video games to train in the use of the heuristic. The first was an adventure game, based on the theory of narrative engagement, and the second was a puzzle- based game, based on the theory of analogical reasoning, using comparisons to help train the learners on applying decision principles. Both games incorporated feedback on diagnostic errors and how they could be corrected. Results showed that both games had positive effects on trauma triage, whereas traditional medical education had none.

Training to improve visual perception skills

In radiology, diagnostic errors fall into two broad categories: perceptual errors, in which an abnormality on an image is not seen or identified, and interpretive errors, in which an abnormality is seen but the meaning or the importance of the finding is not correctly understood.

Perceptual errors account for a majority of misdiagnoses in radiology and can be rooted in faulty visual processing or, to a lesser extent, cognitive biases.

Improving visual perception skills, which predominate the diagnostic process in radiology, requires methods of training different from those to improve clinical reasoning. Four studies evaluated the impact of educational interventions on perceptive skills, with three showing improvement in perceptive performance. The studies involved subjects early in their medical training, and each tested a different intervention to improve perceptive performance.

A novel study by Goodman and Kelleher (2017) took 15 first-year radiology residents to an art gallery, where experts with experience in teaching fine art perception trained the residents on how to thoroughly analyze a painting.[18] The trainees were instructed to write down everything they could see in the painting, after which the art instructor showed the trainees how to identify additional items in the painting that they had not perceived. To test this intervention, the residents were given 15 radiographs pre-intervention and another 15 post-intervention and asked to identify the abnormalities. At baseline, the residents scored an average of 2.3 out of a maximum score of 15. After the art training, the residents' scores significantly improved, with an average score of 6.3 ($p<.0001$), indicating that perception training may improve radiology residents' abilities to identify abnormalities in radiographs.

Another study evaluated different proportions of normal and abnormal radiographs in image training sets to determine the best case-mix for achieving higher perceptive performance.[19] For the intervention, the authors used three different 50-case training sets, which varied in their proportions of abnormal cases (30%, 50%, 70%). One hundred emergency medicine residents, pediatric residents, and pediatric emergency medicine fellows were randomized to use one of the training sets. After the intervention, all participants completed the same post-test. All three groups showed improvement after the intervention, but with varying sensitivity-specificity trade-offs. The group that received the lowest proportion (30%) of abnormal radiographs had a higher specificity and was more accurate with negative radiographs. The group that trained on the set with the highest proportion of abnormal radiographs (70%) detected more abnormalities when abnormalities were present, achieving higher sensitivity.

These findings have significant implications for medical education, as it may be that case mix should beadjusted based on the desired sensitivity or specificity for a given examination type (e.g., screening exams vs. diagnostic test). The use of cognitive training interventions, such as reflective practice, may yield the greatest improvements for only the most complex diagnostic cases. This makes application of appropriate strategies in actual clinical settings difficult, as whether a case is complex is often not determined until after the diagnostic process has begun. In addition, some of these teaching techniques, such as those using standardized patients or requiring development of simulations, are labor intensive and may not be generalizable.

Peer review

Peer review is the systematic and critical evaluation of performance by colleagues with similar competencies using structured procedures. Peer review in clinical settings has two recognized objectives: data collection and analysis to identify errors; and feedback with the intention of improving clinical performance and practice quality. It also serves to fulfill accreditation requirements, such as The Joint Commission requirement that all physicians who have been granted privileges at an organization undergo evaluation of and collect data relating to their performance, or the American College of Radiology physician peer review requirements for accreditation. When done systematically and fairly, peer review contributes to and derives from a culture of safety and learning.

Peer review, when designed appropriately, has the potential to achieve patient safety goals by having an impact on care either directly at the time of testing (e.g., identifying and resolving the error before it affects the patient) or indirectly by improving physician practice through continual learning and feedback.

Traditional peer review: random versus nonrandom selection

Evaluation of professional practice, which can be accomplished through peer review, is a requirement for accreditation by organizations such as the American College of Radiology (ACR) and The Joint Commission, and recommended by professional associations such as the College of American Pathologists. The best-known example is that used in radiology, the ACR's RADPEER program, which is a standardized process with a set number of cases targeted for review (typically 5%) and a uniform scoring system. The cases, which are originally interpreted images being used for comparison during a subsequent imaging exam by the reviewing "peer" radiologist, are randomly selected and scored. Scores are assigned based on the clinical significance of the discrepancy between the initial radiologist's interpretation and the review radiologist's interpretation: (1) concur with interpretation; (2) discrepancyin interpretation, correct interpretation is not ordinarily expected to be made (i.e., an understandable miss); and (3) discrepancy in interpretation and the correct interpretation should be made most of the time. Scores of 2 and 3 can be modified with an additional designation of (a) unlikely to be clinically significant or (b) likely to be clinically significant.

Scores of 2b, 3a, or 3b are reviewed by a third party, typically a department chair, medical director, or quality assurance committee. Discrepancy rates can then be calculated for individual radiologists and used for comparison against peer groups or national benchmarks, and for improving practice. Discrepancy rates are typically relatively low (range 0.8% - 3.8%% in a review of 6 studies of randomly-selected images.

Double reading

A common form of nonrandom peer review, particularly in radiology practice, is the use of double reading, in which a second clinician reviews a recently completed case. With this method the review is integrated into the diagnostic process rather than conduced retrospectively, allowing errors to be identified and resolved prior to a report being transmitted to the ordering provider or the patient.

Geijer and Geijer (2018) reviewed 46 studies to identify the value of double reading in radiology.[20] The studies fell into two categories: those that used two radiologists of similar degree of sub-specialization (e.g., both neuroradiologists) and those that used a subspecialized radiologist only for the second review(e.g., general radiologist followed by hepatobiliary radiologist). Across both types of studies included in the review, double reading increased sensitivity at the expense of reduced specificity. In other words, double reading tended to identify more disease, while also identifying disease in cases that were actually negative (i.e., false positives). With discrepancy rates in studies between 26% and 37%, the authors suggest that double reading might be most impactful for trauma CT scans, for which there are a large number of images generated that need to be read quickly under stressful circumstances. The authors also suggest that it may be more efficient to use a single subspecialized radiologist rather than implement double reading, as using a subspecialist as a second reviewer introduced discrepancy rates up to 50%. This was thought to be a result of the subspecialist changing the initial reports and the bias introduced by having the subspecialist being the reference standard for the study.

In the case of dual reading, Natarajan et al. (2017) found that the addition of the radiologist interpretation to the orthopedic interpretation of musculoskeletal films in pediatric orthopedic practice added clinically relevant information in 1% of the cases, yet misinterpreted 1.7% of the cases, potentially adding diagnostic errors into the process.[21] Murphy et al. (2010) found that double reading of colon CT scans increased the number of individuals falsely diagnosed with colon pathology.[22] The protocol found one extra-colonic cancer, but at the expense of five unnecessary endoscopic procedures.

On the other hand, Harvey et al. (2016) identified that their group-oriented consensus review method had a secondary effect of fostering a culture of safety in their department, where radiologists feel comfortable identifying and openly discussing diagnostic errors.[23] This finding was supported by Itri et al. (2018), who recognized that peer learning conferences, during which diagnostic errors were reviewed, supported a culture of safety where clinicians learned from their mistakes.[24]

Several studies found that certain more complex radiology cases, such as trauma scans or MRIs, benefited more from double reading when compared with examinations such as plain musculoskeletal radiographs. Recommendations include the use of subspecialty reinterpretation of high-risk cases, such as in patients with history of cancer or trauma, or using data from peer review to identify areas where there are more likely to be missed diagnoses and focusing peer review on those areas.

Concerns over maintenance of confidentiality by the physicians and fears about the impact of peer review findings on medical malpractice litigation have been identified as a barrier to participation in peer review. One way to overcome this challenge is to deliberately design programs to ensure that all information disclosed through the process of peer review is protected under a state's statutory peer review privilege, preventing the information from being used against a clinician in malpractice claims. All 50 States and the District of Columbia have privilege statutes that protect peer review records of medical staff members, although how the privilege is applied may vary by state.

Traditional random peer review mechanisms employed to maintain compliance with accreditation requirements have not consistently been demonstrated to improve diagnostic accuracy. There is also a need to identify the root causes of discrepancies so that they can be understood and prevented. Discrepancies that are generated because of poor image or specimen quality will be addressed very differently from those that are a result of a lack of time or knowledge by the clinician.

Summary of diagnostic errors

The patient safety practices reviewed in this section aim to reduce diagnostic errors by targeting cognitive-based factors and systems-based factors. The evidence in support of these practices varies in depth and consistency. CDS offers solutions to address diagnostic errors through incorporation of evidence-based diagnostic protocols, and improve communication and integration with clinical workflow. This review found that CDS may improve diagnosis, although the studies tend to be exploratory in nature, validating the decision algorithms. The use of AI and machine learning has generated excitement over its potential, but they are also exploratory and lack testing during the care of actual patients. These systems need to be reassessed once fully implemented and iteratively improved in real clinical settings on patients actively undergoing diagnosis. Studies included in the review also support the notion that CDS tools are best used as adjuncts to the clinician's decision making process and not as replacements. This was particularly true for CDS tools that assist with diagnostic study interpretation, such as ECG interpretation. The literature also identified that the diagnoses generated by CDS tools are only as good as the information that is put into the system; if the initial assessment of the patient (e.g., physical exam finding) is incorrect, it is likely that the output will be incorrect.

RNSs aim to address lapses in communication, a contributing factor to delayed diagnosis and treatment of patients in both ambulatory and inpatient settings. For both critical and non-critical CSTR of radiologic studies, lab studies, and tests pending at discharge, the use of RNS showed mixed results in the timeliness of receipt and in action on the test results. Policies and procedures that aligned with the system, mindful integration of the RNS into the existing workflow, and appropriate staffing were identified as factors supporting successful implementation of the systems.

Evidence to support education and training on the diagnostic process to enhance clinical reasoning and decrease biases showed generally positive results, with study designs being strong (e.g., randomized controlled trials), although there was some lack of generalizability, as many of the studies had low numbers of subjects. Training on metacognitive skills as a way to reduce biases may improve diagnostic accuracy, particularly as clinical experience increases. Online training, either didactic or simulation based, was shown to be successful at improving clinical reasoning skills.

Studies of peer review show significant numbers of missed or misread test interpretations. However, there is a lack of evidence to show that traditional random peer review and feedback mechanisms used in radiology or pathology to maintain compliance with accreditation requirements improve diagnostic quality over time or prevent diagnostic errors from reaching the patient. For both radiology and pathology, nonrandom peer review appears to be more effective at identifying diagnostic errors than random peer review; and when peer review is conducted prospectively, there is an opportunity to identify diagnostic errors before they reach or harm the patient.

Overall, there is still a relative dearth of studies focused on diagnostic error prevention and methods to improve diagnostic accuracy compared with other patient safety topics. General considerations for future research in diagnostic safety include the use of consistent measures and definitions of diagnostic error to allow comparisons of studies and aggregation of data across smaller studies (i.e., meta-analyses), moving from exploratory studies to studies conducted in real clinical settings in real time, and understanding how to best integrate technology with the current workflow to support diagnosis-related activities.

Failure to rescue

Failure to rescue (FTR) is failure or delay in recognizing and responding to a hospitalized patient experiencing complications from a disease process or medical intervention. As a patient safety and healthcare quality metric, FTR is typically defined as mortality following a complication, although there is no universally agreed upon definition and slight variations exist between institutions. This section reviews two patient safety practices that have been widely implemented to address FTR: patient monitoring systems (PMS) and rapid response teams (RRTs).

Failure to rescue is a well-established issue in patient safety and healthcare quality. Over the past two decades, there have been numerous studies identifying clinical antecedents to in-hospital mortality as well as strategies to respond to these events. Silber and colleagues were the first to use the term as a metric for safety and quality in their 1992 study hypothesizing that FTR might be associated more with hospital characteristics than with patient illness severity.[25] Since then, many studies have investigated the variations in patient outcomes following in-hospital complications and in 2005, the Institute of Healthcare Improvement's 100,000 Lives campaign identified FTR as one of six key safety initiatives, estimating that implementation of rapid response systems could save 66,000 lives.[26] Because in-hospital complications can occur to any patient regardless of their diagnosis or disease process, FTR represents a ubiquitously significant problem and is therefore an important indicator of care quality.

Rapid response systems (RRSs) are hospital-based systems to detect and treat deteriorating patients before adverse events occur. They have emerged as an intuitive approach to address the two core contributors to FTR: failure in adequately monitoring and identifying and failure in responding to hospitalized patients who are at high risk for rapid clinical deterioration.

Patient monitoring involves assessment of various vital signs and physiological changes. Monitoring criteria are then used to help guide activation of the RRT. Although there is no universal standard, most rapid response call criteria include abnormalities in physiologic measures such as respiratory rate, heart rate, systolic blood pressure, oxygen saturation, and urine output. Additional criteria may include staff member or family member concern about the patient's condition, mental status changes, or uncontrolled pain.

Once activated by the monitoring staff, the RRT then responds to the patient to prevent avoidable morbidity and mortality. Other models exist, including medical emergency teams and critical care outreach. This section uses "RRT" as an umbrella term, as all models are conceptually united by the goal of early intervention for patients who are at high risk for clinical deterioration. The RRT is typically multidisciplinary and can consist of a nurse, physician, and respiratory therapist, although team composition may vary depending on institutional policy and guidelines. They are able to assess the patient, diagnose, provide initial treatment, and rapidly triage the patient. Patients can then transfer to a higher level of care (i.e., intensive care unit), have their care returned back to the primary medical team, or have their treatment plan revised. Specialized resources such as cardiac arrest teams or stroke teams are considered separate from the RRT and may be involved in the care of the patient, if warranted.

Driven by quality and safety requirements as well as recommendations, a swift uptake in RRTs has been noted in the United States and Australia, and is increasingly seen in other developed countries.

Because use of RRT is now so widespread, it has become difficult to produce high-quality, randomized controlled trials, and that causes apprehension in those who advocate for a more rigorously studied and evidence-based intervention.

Patient monitoring systems

Early clinician recognition of signs of patient deterioration is critical to reducing the risk of preventable death and other adverse events. While RRTs have been widely implemented, their success depends on recognizing a deteriorating patient before serious harm has occurred. Patient monitoring system (PMS) is an umbrella term for electronic systems that scan patient data (e.g. vital signs and other variables) for signs of deterioration and alert a clinician if certain criteria are met. These systems can decrease the time from the onset of deterioration to the initiation of treatment, increasing the potential for better patient outcomes.

While the training and clinical reasoning of staff cannot be discounted, PMSs can provide a valuable counterpart and backstop to ensure that no deteriorating patients are missed. Patients who are at a high risk of deterioration are usually admitted to a critical care setting or a telemetry unit, where patient vital signs are continuously monitored (CM) and there is a low patient-to-nurse ratio. However, most hospital beds are outside of these intensive settings, and most patients are boarded in general medical and surgical wards. These units typically do not have continuous PMS, and rely on intermittent collection of patient vital signs on a predetermined schedule (e.g., every 4–6 hours) and on nursing activation of the RRT. A delay of several hours in recognizing a patient's deterioration can lead to avoidable morbidity, ICU transfers, and mortality. This section will review patient monitoring systems that use CM devices (e.g., pulse oximetry monitors), as well as electronic monitoring of intermittent manually collected vital signs.

Effect on process measures

Although testing a PMS for its effect on outcome measures (e.g., mortality) is the ultimate goal of this PSP, it is also important to test whether the PMS improves processes of care for deteriorating patients. Seven of eight studies reported one or more process measures for PMSs, all of which took place in general medical/surgical units. Articles assessing an effect on process measures had a variety of study designs, with one randomized trial and six experimental studies of varying type. In addition, one systematic review addressed this topic.

The most commonly reported process measure in the reviewed articles was the number of rescue events, including RRT calls or Code Blue calls (i.e., calls activated by healthcare professionals in the hospital when there is a patient in cardiac or respiratory arrest). It is unclear how to interpret this measure in relation to the PMS. A decrease in rescue events likely indicates that more deteriorating patients are discovered early and are stabilized by staff without needing to call the RRT. It could also indicate that patients in decline are being missed. Ultimately, this process measure needs to be combined with outcome measures to understand its true effect. Other reported process measures were related to vital sign collection times.

A systematic review and meta-analysis by Cardona-Morrell and colleagues reported that implementing a PMS with CM was not associated with a reduction in mortality (odds ratio [OR]=0.87, 95% CI 0.57–1.33), while PMS with IM was associated with a statistically significant but modest reduction in mortality (OR=0.78, 95% CI 0.61–0.99).[27] This may seem counterintuitive, but the authors note that studies included in the meta-analysis were heterogeneous and most were observational. They conclude that more studies are needed of both CM and IM systems before drawing a definitive conclusion. Four other studies not included in that systematic review found no impact on mortality. Several studies noted that a generally low mortality rate before and during their studies made it unlikely that they could detect a significant change without a large increase in the sample size.

Study authors did not indicate many unintended negative consequences as a result of implementing a PMS to detect patient deterioration. Some expressed hypothetical concern raised of over-testing and over-treating patients, but no studies measured outcomes to test these. If the PMS has a low predictive value, patients who are not deteriorating could receive unnecessary treatment or be transferred to a higher level of care as a result. However, this risk can be mitigated by ensuring the use of a highly predictive system.

Positive consequences were mentioned by several authors. The tracking and display of patient vitals gave nurses and other clinicians a sense of increased knowledge about their patients. It also allowed the RRT and other primary team members to take a proactive approach to patient care, rather than relying solely on nursing staff activating an RRT call. Authors also noted that when nurses did call for an RRT, the system allowed them to communicate their concerns about a patient with objective, quantifiable data. Other potential benefits included nurses spending more time on patient-centered tasks and less time on vital sign collection, and reduced reliance on RRTs. The latter is supported by several studies that found a decrease in rescue events after PMS implementation.

Implementing a PMS can be difficult technologically, financially, and in terms of workflow changes for staff. The studies we reviewed identified factors that facilitate PMS implementation, as well as barriers to successful PMS implementation.

A PMS will be effective only if it is both sensitive and specific, to engender clinician trust and reduce false-positive alerts. When a PMS identifies a deteriorating patient, clinicians who can respond need to be quickly notified. Study authors disagreed on the best method for communicating this need to clinicians. Some favored auditory and visual alerts, and others preferred a non-interruptive dashboard at both the bedside and a central station to reduce potential alert fatigue.

Good communication between the bedside clinicians and the RRT was also cited as a facilitator, as well as staff who are well trained and have strong clinical reasoning. Finally, in relation to cost, several PMS systems are now available as electronic health record add-on modules or as standalone systems, sparing hospitals the cost of designing, building, and testing a system.

The nonspecific nature of patient deterioration makes achieving a highly predictive system difficult. Therefore, it is important for clinicians/administrators to test system performance and adjust variable thresholds to best balance speed, sensitivity, and specificity for their setting. For example, some settings may be willing to accept a lower sensitivity to reduce alarm fatigue.

A poorly-designed system that is difficult to use can be a barrier. However, even in a well-designed system, staff need to understand the potential value of the PMS, be trained to use it correctly, understand the alerts/indicators it generates, and know how to respond quickly (calling the RRT or activating a Code Blue). A PMS will improve outcomes only if accompanied by comprehensive procedures for escalation, RRT activation, and audit and feedback to staff.

Some PMSs that require manual input of vital signs into the electronic health record can actually delay vital sign recording and recognition of patient deterioration. Insufficient computers to input data and the practice of busy staff taking vital signs but delaying entry of the data were cited as barriers. Finally, the cost of designing, implementing, and storing data for a PMS can be prohibitive for smaller facilities.

Rapid response teams

Brought to widespread attention by the 2005 Institute for Healthcare Improvement's 100,000 Lives Campaign, the RRT was developed in response to a growing body of evidence that revealed deficienciesin responding to rapid clinical decline in the inpatient setting. A key principle underlying RRTs is that early intervention can prevent avoidable morbidity and mortality in the non-intensive care hospital setting. RRTs have since been widely implemented across the globe.

RRTs act as the efferent limb of the RRS and include the clinical care team that responds to the afferent limb's calls. This team is typically multidisciplinary, and consists of a nurse, a physician, and a respiratory therapist, although team composition may vary slightly depending on institution policy and guidelines. The RRT assesses patient disposition, which can result in transfer of the patient to the ICU, return of care back to the primary medical team, or revision of the treatment plan.

Of the three meta-analyses that reported the impact of RRS implementation on overall hospital mortality, two found significant decreases in mortality rates.[28,29] Chan et al., using 15 adult and pediatric studies with considerable heterogeneity found no difference in overall hospital mortality.[30]

A subgroup analysis of the four pediatric studies did show significant decrease in hospital mortality (RR, 0.79; 95% CI, 0.63-0.98), but significant heterogeneity was observed. Without a control group in most studies, it is difficult to draw conclusions about causality. This is especially true for the overall hospital mortality rate, which Solomon et al. note has been falling since 2000. This trend may confound the results of studies that observed decreases in hospital mortality rate following RRT implementation.

Indeed, Chen et al., in a 2016 study assessing the impact of RRT implementation across New South Wales, Australia, found that overall hospital mortality rates and cardiac arrest rates had decreased in the 2 years prior to RRT implementation.[31] There were no significant changes in these trends once an RRT had been implemented. However, there was a significant decrease in mortality among patients with low mortality risk. This decreased mortality rate was attributed to RRT prevention of cardiac arrests, suggesting that the low-risk population is where future RRT implementation may have the most impact.

Successful implementation of an RRT requires adoption by both monitoring and response teams, whichmay be influenced by cost, team composition, and staff perception. The benefits from RRT implementation may become apparent only after the RRT has been in place for some time. Moriarty et al. saw significant findings beginning in the second year following response team implementation.[32] However, these changes coincided with the institution's efforts to educate nursing staff as well as to increase positive perception of the RRT, suggesting that educational efforts, rather than time, drive lasting culture and process changes.

Cultural barriers and traditional hierarchical models of patient monitoring and rapid response may prevent successful implementation of RRTs. For example, Moriarty et al. suggest that the monitoring team may hesitate to activate the response team in fear of the call being viewed "as an acknowledgment of inadequacy on their part." Just as a culture of clear communication and teamwork can help to facilitate successful RRT implementation, one that discourages speaking up and instead supports a hierarchical structure can impede both perceptions and use of an RRT.

The RRT is dependent on the monitoring team's engagement, perception, and activation of the RRT. While all included studies detail criteria for activation of the RRT, the actual mechanism of the activation process is often left undefined, without clear descriptions of who participates, what the process involves, or whether activation is mandatory versus voluntary. One study found that changing the activation mechanism from a voluntary to a mandatory call based on physiologic criteria resulted in a statistically significant decrease in cardiopulmonary arrest rates. This suggests that voluntary activation may present a barrier to successful RRT use, while mandatory activation may act as a facilitator. Further research on this topic is needed.

Conclusions

The PSPs reviewed in this chapter aim to reduce FTR by addressing two of its core components: failure to identify and failure to respond to hospital patients who are at risk for rapid clinical deterioration. Thisreview finds that implementation of continuous patient monitoring may decrease rescue events and hospital length of stay but not mortality, while IM shows a moderate but inconsistent effect on mortality. It remains unclear whether RRT reduces mortality or ICU transfer rates. Together, these findings suggest that both the afferent and efferent arms of the rapid response system decrease in-hospital adverse events but not overall mortality. Many studies were observational and had an increased risk for bias, indicating a need for more rigorous, high-quality studies.

Findings in both PSPs suggest that an RRS is most successful when there is effective and efficient communication. The electronic monitoring system, bedside staff, and rapid response staff are all susceptible to communication breakdown, and all points along the RRS pathway warrant careful consideration when deciding to implement an RRS. This requires not only education and training but also technical care so as not to create alert fatigue, as well as a cultural shift to support rather than discourage speaking up. Finally, very few studies comment on RRT activation, which is an important bridge connecting the RRS's identification of deterioration and the response to prevent harm. A better understanding of the mechanism and components of this process may elucidate further interventions for minimizing FTR.

Alarm fatigue

Alarm fatigue occurs when clinicians experience high exposure to medical device alarms, causing alarm desensitization and leading to missed alarms or delayed response. As the frequency of alarms used in healthcare rises, alarm fatigue has been increasingly recognized as an important patient safety issue. Although the problem of alarm fatigue has been well documented, alarm-related events are often underreported, and there is still limited research examining interventions to address the issue. This section reviews two system-level patient safety practices that aim to address alarm fatigue: safety culture and risk assessment.

Addressing alarm fatigue through improving safety culture involves system-wide interventions, such as leadership ensuring that there are clear processes in place for safe alarm management and establishing practices to share information about alarm-related incidents and prevention strategies. The literature provides moderate evidence for reduction in total alarms and noise level following the implementation of features of safety culture. Surveys assessing nurses' perceptions of alarm fatigue and behavior changes regarding alarm management showed mixed results; however, two studies reported perceived reduction in alarm fatigue. More high-quality studies are needed to test the effects of safety culture elements on process and outcome measures related to alarm fatigue.

Performing baseline alarm risk assessments is an important step in order to understand current needs and conditions contributing to alarm fatigue. Conducting an alarm risk assessment can include evaluating medical devices and computer systems, analyzing data from clinical event reporting systems,and assessing patient satisfaction and the physical environment. There is currently limited research studying the impact of conducting alarm risk assessments on reducing alarm fatigue. Studies have generally examined alarm risk assessments as a component of larger quality improvement (QI) projects or system-wide initiatives and they provide moderately strong evidence supporting the use of multidisciplinary teams to conduct these assessments.

Background

Healthcare continues to become increasingly computerized, and clinicians use an assortment of equipment and technology to monitor patient conditions. Most healthcare devices provide auditory or visual warnings intended to alert clinicians when a patient's condition deviates from a predetermined normal range. Many device alarms emit different sounds, tones, and/or pitches depending on the level of severity (i.e., advisory vs. warning vs. crisis alarms) to help clinicians determine how to respond.

System status or non-clinical alarms can also occur and are caused by mechanical or electrical problems, such as a device needing new batteries. Device alarms can be an important tool to assist in clinical decision making; however, alarms can become hazardous to patient safety if excessive alarm frequency coupled with high prevalence of false alarms leads to alarm fatigue.

Alarm fatigue occurs when clinicians, especially nurses, become desensitized to safety alarms due to the sheer number of alarm signals, which in turn can lead to missed alarms or delayed response. Alarm desensitization is compounded by the fact that false or nonactionable alarms occur frequently. False alarms are those that occur in the absence of an intended valid event, and nonactionable alarms occur when an alarm system works as designed but signifies an event that is not clinically significant and/or requires no additional intervention. The high volume of these nuisance alarms is not only disruptive, but also creates a situation where staff doubt the reliability of alarms and as a result turn down the volume, ignore, or deactivate the alarms. This adversely affects patient safety because clinicians are not only ignoring the nuisance alarms, but also ignoring or missing many clinically significant and actionable alarms.

Alarm fatigue is increasingly recognized as a critical safety issue, and alarm management has become a priority for improvement in hospitals. From 2005 to 2008, the U.S. Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience (MAUDE) reporting system received 566 reports of patient deaths related to monitoring device alarms.[33]

Alarm fatigue was a major contributor to these events due to the excessive number of alarms and high percentage of false alarms. A study at a major academic medical center found a total of more than 59,000 alarms over a 12-day period, while another study found 16,953 total alarms over an 18-day period on a single medical unit.[34] Studies have shown that the percentage of false alarms can range from 72 percent to 99 percent.[34]

Safety culture

Establishing a culture of safety is essential to improving overall healthcare quality. Broadly, key features of safety culture include: acknowledgment of the high-risk nature of an organization's activities; a blame-free environment where individuals are able to report errors without fear of punishment; encouragement of collaboration across staff levels and disciplines to seek solutions to patient safety problems; and an organizational commitment of resources to address safety concerns. Addressing alarm fatigue through improving safety culture can involve a variety of interventions that are often implemented as a system-wide or unit-wide initiative. Examples of these elements include the following: leadership ensures there are clear processes in place for safe alarm management and response; leadership establishes priorities for the adoption of alarm technology; and at all staffing levels, practices are established to share information about alarm-related incidents, prevention strategies, and lessons learned. This section reviews efforts to address alarm fatigue through improving safety culture; clinical outcome measures and provider perceptions, as well as barriers and facilitators to implementation, are examined.

Improving the culture of safety in a unit or hospital can be difficult, and this PSP includes a variety of interventions involving commitment to a culture of safety by all staff at all levels, as well as changes to processes, workflows, and policies that embody this commitment. Across these varied initiatives, some common themes of facilitators and barriers emerged.

Facilitators

Buy-in, especially from leadership, can greatly facilitate an effective change in safety culture. In addition to leadership commitment, securing buy-in from staff at all levels facilitates culture change. An important step in improving care is changing the culture to recognize that patient safety is everyone's responsibility and each staff member has the duty to address alarms. Cultural change is often necessary throughout a unit to transition from alarm management being considered a nursing concern, to everyone taking responsibility for alarm management. Standardized procedures are also important for supporting a safety culture.

BEFORE MOVING ONTO THE NEXT SECTION, PLEASE COMPLETE CASE STUDY 2.

Case Study 2: Alarm Competency

Instructions: Spend 10 minutes reviewing the case below and considering the questions that follow.

Kate Hileman, RN, MSN, knows all too well the reality behind the role alarm management plays in patient care delivery having worked as a staff nurse at the University of Pittsburgh Medical Center's Presbyterian Hospital, which is known for organ transplantation, cardiology care, cardiovascular surgery, critical care medicine, neurosurgery, and trauma services.[35]

"In 2006, following a particularly difficult shift, I met with the staff nurses for a debriefing," Kate says. "We began discussing some of the challenges they were facing on a daily basis, and we made a list of the things they saw as barriers to providing consistent quality nursing care. It was then that the issue of excessive alarm noise came up,"

The nurses, particularly on the night shift, acknowledged that alarm noise consistently pulled them away from direct patient care and that often alarm signals were too numerous for them to be able to respond in a timely fashion. Kate and a team of nurses immediately began work on a pilot project that examined the number and types of alarm signals that were occurring. They began by doing direct observations on the unit by shadowing nurses as they worked, tracking the number of alarm conditions and related signals, and their responses to them. One observer was stationed at the central monitor station and recorded all the alarm signals and corresponding conditions which occurred during an eight hour shift. They also analyzed data from the main central monitoring station to determine the number of life-threatening and non-life-threatening alarm conditions.

"The results were eye opening," says Kate. "The mid-level, non-life-threatening arrhythmia alarm conditions accounted for the majority of all alarm signals during an initial ten-day observation period and ranged anywhere from 247 to 1565 signals per day on an 18 bed medical cardiology unit. The overall average for the total observation period was 871 non-life threatening/non-actionable alarm signals per day."

The alarm signals had become background noise for nurses and other hospital staff members who have become desensitized to alarm sounds. In response to the data, non-life threatening informational alarms were set to "OFF," permitting only heart rate parameters and life-threatening arrhythmias to produce an alarm signal. Nurses were then taught how to customize individual alarm signals based on a patient's clinical conditions. Recognizing the challenge in customizing alarm signals for individual patients due to the lack of standardized protocols that exist today, UPMC established its own protocol consisting of "Eight Critical Elements" and an annual nursing competency review.

As a result of these efforts, overall alarm signal time was reduced by approximately 80%. Since this protocol was put in place, there has been no increase in adverse patient events related to the reduction of alarm signals on non-life threatening cardiac arrhythmias.

1. **Is alarm fatigue such as described in this case study a problem at your place of work?**_____

2. **Do you think the measures taken to reduce alarm fatigue at UPMC might work in your workplace setting?**_____

3. **How have you, personally, adapted to the presence of alarms of various sorts during your daily clinical work?**_____

Risk assessment

Risk management is crucial to promoting safer healthcare and proactively identifying, prioritizing, and mitigating patient safety risk. Many national organizations recognize that conducting a baseline alarm assessment to understand current needs and conditions contributing to alarm fatigue is an important step in alarm management. For example, the AAMI Foundation recommends engaging a multidisciplinary team to prepare an alarm inventory risk analysis and gap analysis that identifies patient safety vulnerabilities that could be amenable to change.[35] An additional element is to identify the most important alarm signals to manage based on: input from the medical staff and clinical departments; risk to patients if the alarm signal is not attended to or if it malfunctions; whether specific alarm signals are needed or unnecessarily contribute to alarm noise and alarm fatigue; potential for patient harm based on internal incident history; and published best practicesand guidelines.

Conducting an alarm risk assessment can include evaluating medical devices and computer systems, including the default alarm settings; assessing patient satisfaction (e.g., sleep interruption from nuisance alarms); and assessing the physical environment to determine whether clinically significant alarm signals are audible to staff. In addition, healthcare settings may use data from event reporting systems to identify actual or near-miss harm reported by staff as a method of risk assessment.

Conclusions about alarm fatigue

The two PSPs reviewed in this section aim to address alarm fatigue by implementing hospital- or unit- wide initiatives to target nonactionable, nuisance alarms and decrease overall alarm burden. The review of evidence shows that implementing elements of safety culture can lead to a decrease in the total number of alarms, number of false alarms, and overall alarm noise level; however, since these initiatives often involve multiple components, it is difficult to know which intervention(s) have the greatest impact. The evidence also shows moderately strong support for conducting risk assessments to understand the current state of alarm management and identify which alarms are the greatest contributors to alarm fatigue. The results of these risk assessments should be used to inform the implementation of processes for safe alarm management and priorities for adoption of alarm technology. Investing in training and education for care providers on new technology as well as ensuring buy-in at all levels and engaging multidisciplinary teams are key to effectively implementing these strategies to reduce alarm fatigue.

Sepsis recognition

Sepsis has been a leading cause of hospitalization and death in U.S. healthcare settings for many years, and accounts for more hospital admissions and spending than any other condition. As a result, preventing, diagnosing, and treating sepsis effectively has been a focus of patient safety and public health in recent years. This section discusses two patient safety practices that aim to identify signs of sepsis and septic shock as quickly as possible so that treatment can be started: manual screening tools and electronic patient monitoring systems (PMSs).

Screening tools are manually administered paper or electronic forms that guide clinicians through a set of criteria as they are assessing a patient. The screening process is administered either at a care transition (e.g., presentation at the emergency department [ED] or to emergency medical services [EMS]) or at regular intervals (e.g., the start of every nursing shift). Current evidence indicates that performance (sensitivity/specificity) of the tools varies, especially in the prehospital setting. Evidence for process measure improvement (i.e., time to initiation of treatment) was of moderate strength in both the hospital and prehospital setting. Evidence for outcome measure improvement was sparse but showed a trend toward improvement. More high-quality studies are needed in diverse settings to test the effects of sepsis screening tools.

Automated systems continuously monitor patient status, such as vital signs, and alert a clinician if criteria for possible sepsis are met. These systems are becoming more widespread, especially in hospitals, which have sophisticated technology infrastructures. While the studies were inconsistent, there appears to be evidence of moderate strength in the current literature for improvement in both process and outcome measures for PMSs. More high-quality studies are needed to confirm these findings, and to identify implementation best practices and lessons learned.

Background

Sepsis is a syndrome of life-threatening organ dysfunction due to a person's systemic dysregulated response to infection. Sepsis can be caused by many types of infection (bacterial, fungal, and viral) and can affect any age group, from neonatal to geriatric. It is a common reason for hospital admission and readmission, with an estimated incidence of 6 percent of all hospital admissions, or more than 1 million admissions in the United States every year.[36] Sepsis also has one of the highest mortality rates of any hospital condition, estimated at 15–30 percent. Tracking incidence and mortality over time is challenging due to shifting definitions and an increasing awareness of sepsis. Some studies show an increase in incidence and a decrease in mortality in recent years, but some show no significant change in either. Among subgroups, older adults and nursing home residents are much more likely to develop and die from sepsis compared with younger adults and non-nursing home residents. In 2013, $24 billion was spent treating sepsis, more than any other condition treated in U.S. hospitals.[37]

The symptoms of sepsis (e.g., high temperature, high blood pressure) are shared by many other conditions, making sepsis difficult to diagnose, especially in the early stages. In addition, sepsis can start suddenly and quickly lead to organ dysfunction and death. In response to this, international organizations such as the Society for Critical Care Medicine have focused on addressing the two problems that sepsis presents: delay in recognition and diagnosis of sepsis, and delay in start of treatment, which combined contribute to the high mortality rate for sepsis.

The need for early recognition and rapid treatment have led to guidelines about how to treat septic patients, with aggressive interventions and timeframes. The most commonly adopted of these is the Surviving Sepsis Campaign (SSC) bundle, which has gone through many iterations, and includes starting broad-spectrum antibiotics and intravenous (IV) fluids, and obtaining blood culture and lactate measurements within a 1- to 6-hour timeframe.[38] Many government agencies across the world have proposed measuring and evaluating hospital compliance to strongly encourage its use. Most notably, since October 2015, the Centers for Medicare & Medicaid Services requires U.S. hospitals to report their performance on a composite process-of-care measure for severe sepsis and septic shock, and ties reimbursement to the measure results.

There is occasionally tension between the goals of antibiotic stewardship and sepsis guidelines, with the former focused on reducing inappropriate use of broad-spectrum antibiotics, and the latter requiring rapid and barrier-free initiation of broad-spectrum antibiotics. Clinicians sometimes perceive antibiotic stewardship goals as being purely restrictive, thereby creating tension in decisions about antibiotics; however, good antibiotic stewardship encompasses appropriate administration of antibiotics, including when there is clinical suspicion for severe sepsis or septic shock. In addition, many clinicians have apprehension about the IV fluid level due to the risk of fluid overload.

The need to diagnose sepsis unambiguously and quickly has led to development of various diagnostic criteria. The signs and thresholds used in these criteria vary but always include at least one vital sign with abnormal thresholds (heart rate [HR], respiratory rate [RR], blood pressure [BP], temperature, etc.), and sometimes include clinical assessments (mental status, suspicion of infection) and laboratory results (lactate, creatinine). The most commonly used criteria are the qSOFA (quick Sequential Organ Failure Assessment), the NEWS (National Early Warning Score), and the increasingly abandoned SIRS (systemic inflammatory response syndrome) criteria.

Sepsis screening tools

Identifying signs of sepsis as early as possible is critical to averting organ failure and risk of death. However, sepsis does not have a simple diagnostic test or specific symptoms that unambiguously indicate onset. International organizations have developed diagnostic criteria and have recommended screening patients at risk of sepsis using these criteria.

Manual paper or electronic tools guide clinicians through the criteria as they assess a patient. The screening process generally takes place either during a care transition (e.g., presentation at the ED or to EMS) or at regular intervals (e.g., the start of every nursing shift). A tool's embedded logic determines if the patient is suspected of having sepsis. If so, the clinician must start treatment as quickly as possible, which has been shown to increase survival.

Prehospital and nursing home

The sensitivity and specificity of prehospital and nursing home screening tools varies widely. Seven of the eight prehospital studies were retrospective and they were addressed in a 2016 systematic review by Smyth and colleagues that found low to very-low quality evidence for the accuracy of prehospital sepsis screening tools.[39] The authors attributed this to lack of EMS personnel training about sepsis and the inaccuracy of using SIRS criteria alone. They conclude that more validation studies are needed to determine the efficacy of prehospital sepsis screening tools.

The ultimate goal of a patient safety practice is to improve the patient outcomes. Three sepsis screening tools were studied prospectively and measured patient outcomes: one in the prehospital setting and two in the hospital setting. All three studies were observational in design and had low to moderately sized samples. The outcomes studied were mortality, ICU admissions rate, and ICU LOS. Attributing improvement in these outcomes to sepsis screening tools is difficult, however, because patients with sepsis are generally older, have multiple comorbidities, and may have advance directives for end-of-life care. In addition, reasons for ICU transfer and ICU LOS are multifactorial and not necessarily correlated with sepsis or the use of a screening tool.

Hunter et al. was the only prehospital study that measured patient outcomes. This study involved an EMS screening tool with a subsequent alert to the hospital; it found a significant reduction in ICU admissions rate (33% with screening vs. 52% without screening, p=0.003), and a non-significant reduction in mortality (11% with screening, 14% without screening, p=0.565).[40]

Hospital

In the hospital setting, Tedesco and colleagues found that a nurse-administered screening tool in the ED of a 320-bed community hospital led to a significant reduction in mortality (18.4% vs. 13.2% days; P = 0.015).[41] Larosa and colleagues implemented an ICU sepsis screening tool in a 673-bed urban teaching hospital and found a significant reduction in mortality after controlling for factors such as mortality in emergency department sepsis (MEDS) score, leucopenia, and age (p=0.01). However, the sample size for this study was quite small (n=58).[42]

Despite the lack of conclusive evidence of effectiveness, use of tools to screen patients for signs of sepsis is widespread due to the urgency for identifying sepsis, and based on guidelines and hospital quality performance measures. However, implementing these tools can prove challenging in terms of resource use and workflow change for staff.

Two common facilitators are education of the clinical staff who will be responsible for administering the screening, and a tool that is easy to learn and use. First, educating nurses and EMS staff about sepsis pathophysiology helps them to better understand and interpret screening parameters, just as these staff are trained to recognize signs of stroke or cardiac arrest. This education may have the additional effect of increasing sepsis care quality, independent of the screening tool itself. Authors stressed that screening tools cannot substitute for the clinical acumen of staff. Second, a tool should be as easy as possible to fit into a clinician's workflow, such as a checklist using a selected number of readily available or routinely collected variables. As a result, lab test results were generally excluded from screening tools. However, it is important to balance the simplicity of a tool and its ease of use with strong sensitivity and specificity. Other facilitators mentioned in these studies included consistent and complete documentation of vital signs on which screening algorithms are based, and standardized use of the tool across hospital units to reduce confusion and communication breakdowns when patients or staff move between units.

Screening every patient for signs of sepsis on a regular basis is labor and time intensive, regardless of the setting. The yield in terms of identifying emerging sepsis may also be low, depending on the prevalence of sepsis in the setting in question. Additionally, the frequency of screening (for example, once per hospital shift) can delay diagnosis of sepsis, defeating the purpose of the screening tool. As a result, transitions of care such as EMS ambulance transport and ED admission are often targeted as optimal times for screening. Other potential barriers include alert fatigue if the tool used is not specific enough, and a possible increase in drug resistance from more and longer use of antibiotics. However, there is no reported evidence about these effects. Finally, without proper training and an easy-to-use tool, adherence by clinical staff may be suboptimal, as reported by O'Shaughnessy et al., diminishing potential benefits.

Sepsis patient monitoring systems

Automated electronic patient monitoring (i.e., surveillance) for signs of emerging sepsis is becoming more widespread, especially in hospitals. Such systems automatically and continuously monitor data from telemetry devices and/or electronic health record (EHR) entries, and alert a clinician if set criteria for sepsis are met. If, after evaluation, a clinician determines that the patient has sepsis, the clinician must start treatment immediately to reduce mortality and improve patient outcomes. The goal is to decrease the time to treatment initiation for sepsis, which has been shown to increase survival.

An automated surveillance system is less time consuming for staff than manual screening for sepsis and alerts clinicians in near real time to a patient's deteriorating condition, more quickly than most manual screening strategies. However, implementing an automated PMS for sepsis can be difficult technologically, financially, and in terms of workflow changes for staff. The studies we reviewed identified supporting factors that facilitate PMS implementation, as well as barriers to successful PMS implementation.

As with manual screening tools, implementing a PMS will be effective only if the system has a high level of sensitivity and specificity, to engender clinician trust and reduce false-positive alerts. To achieve this, some prospective studies iteratively revised thresholds for key values, with input from the clinicians, to optimize tool performance. Some more recent studies used machine learning to optimize system performance. To improve system usability, input from clinicians was solicited in some studies, followed by adaptations. These included allowing a nurse to "snooze" an alert for 6 hours if the patient is already under assessment for sepsis, or implementing a "traffic light" system on a dashboard to visually show clinicians which patients are in a warning zone (yellow) or need urgent attention (red). Other facilitators include: consistent and complete input of vital signs on which the PMS relies, having a specific staff member assigned to receive all alerts and determine if a physician needs to be called, and designing the PMS to work reliably even if data are incomplete. Building an automated PMS from scratch is costly, but several PMS systems are now available as an add-on EHR or telemedicine module, which is more efficient for a hospital than designing and testing a de novo system.

The nonspecific nature of sepsis makes achieving a highly predictive system difficult, whether on paper or in an automated PMS. This is particularly difficult in pediatric settings because the "normal" ranges for vital signs are age dependent and more difficult to fine tune. In addition, if the electronic monitoring and alerting system is poorly designed or difficult to use, it can lead to clinician confusion, frustration, and possibly to worse patient care. For example, if the alert physicians receive contains too little information (or too much), or if the action required is not clear, physicians may find the system too difficult or burdensome to use. Lack of adequate staff training on using the system is also a potential barrier, even if a system has high sensitivity and specificity. Additionally, the cost of designing and implementing a PMS can be prohibitive for smaller hospitals, and while an EHR add-on can reduce cost, it may result in less customizable functionality. Finally, after a system is implemented, refining the algorithm and updating it based on changing sepsis criteria require close work with the facility's IT department, which can be resource and time intensive.

Multicomponent sepsis interventions

Identifying sepsis as quickly as possible is of critical importance to improving outcomes, but there are other areas of sepsis care and management that can improve outcomes, such as test ordering and results delivery, and initiation of treatment following a sepsis diagnosis. In response to this complexity, some institutions have implemented multicomponent quality improvement (QI) programs aimed at improving the full spectrum of sepsis recognition and care. Several studies found in the search results for the PSPs Patient Monitoring Systems and Screening Tools concern such multifaceted QI initiatives.

Many of the barriers and facilitators to the implementation of a multicomponent intervention are similar to those for implementing a screening tool or PMS, including the importance of clinician education to identify signs of sepsis onset and consistent protocols across hospital units. Additional facilitators mentioned in these five studies included strong teamwork among providers, pharmacy staff ensuring initiation of antibiotics. One study found that additional nursing staff and space for triage were needed to overcome delays in diagnosis and treatment of sepsis.

BEFORE MOVING ONTO THE NEXT SECTION, PLEASE COMPLETE CASE STUDY 3.

Conclusions

The two PSPs reviewed in this section aim to reduce the time to recognition of sepsis so that treatment can be initiated quickly, with improvement in important patient outcomes. The review of evidence shows that manual screening tools can improve time to treatment, but the effect on mortality and other outcome measures is uncertain. Such tools may be most useful in non-hospital settings such as EMS and nursing homes, but many more studies are needed to test their effects in these settings. Evidence for PMSs in the hospital setting showed some improvement in both process and outcome measures, especially in non-ICU units. However, many studies were observational in design, limiting their strength and increasing the risk of bias. More rigorous studies are needed to test the effects of these systems.

Implementing a screening tool or PMS for sepsis requires dedicated resources and effective staff training, and it can be costly. Either type of tool can be effective if it demonstrates acceptable and sustained sensitivity and specificity, which requires pre-validation and regular monitoring. A manual screening tool is more time intensive for clinicians, but an electronic PMS may be more costly to implement and more difficult for staff to use. The customizability of a PMS's features (e.g., "snooze" button) can add flexibility to the complexities of sepsis care, but this comes with a higher cost to implement than a manual screening tool. The decision to implement a sepsis recognition PSP, and whether it should be manual or automated, should be based on the needs and constraints of the particular setting rather than a "one-size-fits-all" approach.

Clostridioides difficile infection

Preventing Clostridioides difficile infection (CDI) in healthcare settings is an important U.S. public health priority and has led to new research, guidelines, and reporting requirements. [Note: the Clinical and Laboratory Standards Institute and the CDC transitioned from use of the name *Clostridium difficile* to *Clostridioides difficile*. For the purposes of this activity, the names are synonymous.] While many of the patient safety practices that help prevent a range of healthcare-associated infections (HAIs) also help to prevent the transmission of CDI (e.g., contact precautions), several CDI-specific practices address the unique risk factors, pathology, and transmission of CDI.

Case Study 3: Identifying sepsis in the ED

Instructions: Spend 10 minutes reviewing the case below and considering the questions that follow.

In 2014 clinicians at the University of Washington Medical Center undertook a quality improvement project to improve the early identification of patients with uncomplicated sepsis, severe sepsis, and septic shock presenting to the emergency department (ED).[43]

The three-tiered intervention consisted of:

1. *A nurse-driven screening tool and management protocol to identify and initiate early treatment of patients with sepsis.*
2. *A computer-assisted screening algorithm that generated a 'Sepsis Alert' pop-up screen in the electronic medical record for treating clinical healthcare providers.*
3. *Automated suggested sepsis-specific order sets for initial workup and resuscitation, antibiotic selection and goal-directed therapy.*

A before and after retrospective cohort study was undertaken to determine the intervention's impact on compliance with recommended sepsis management, including serum lactate measured in the ED, intravenous fluid administered within 2 hours of triage, antibiotics administered within 3 hours of triage and blood cultures drawn before antibiotic administration. Mortality rates for patients in the ED with a sepsis-designated ICD-9 code present on admission were also analyzed.

Overall bundle compliance increased from 28% at baseline to 71% in the last quarter of the study. Bundle, antibiotic and intravenous fluid compliance all increased significantly after launch of the sepsis initiative (eg, bundle and intravenous fluid compliance increased by 74% and 54%, respectively. Bundle and antibiotic compliance both showed further significant increases after implementation of suggested order sets (31% and 25% increases, respectively). The mortality rate for patients in the ED admitted with sepsis was 13.3% before implementation and fell to 11.1% after (p=0.230). The authors concluded that "the new protocol demonstrates that early screening interventions can lead to expedited delivery of care to patients with sepsis in the ED and could serve as a model for other facilities."

1. **Thinking about your own institution how effective do you think efforts are to identify and manage patients with sepsis or suspected sepsis? In what ways could that effort be improved?**_____

2. **Do you think the three steps used in this quality improvement project could be realistically replicated in other hospitals? Why or why not?**_____

3. **Which of the outcomes assessed in the study of this intervention do you think is most clinically important, and why?**_____

Background

C. difficile is a contagious bacterium that can cause diarrhea, fever, colitis (an inflammation of the colon), toxic megacolon (a dilated colon that may be accompanied by septic shock), and, in some cases, death. The *C. difficile* bacterium colonizes in the large intestine. In infected patients, toxins produced by the organism cause CDI symptoms, primarily diarrhea and colitis. The most common risk factors for CDI are antimicrobial use, advanced age, hospitalization, and a weakened immune system. *C. difficile* is transmitted through the fecal-oral route and acquisition is most frequently attributed to the healthcare setting.

Complications are common in patients age 65 and older and an estimated 1 in 11 patients 65 and older with healthcare-associated CDI dies within 30 days of CDI diagnosis.[44] Patients with a healthy immune response to the organism can be carriers of *C. difficile* (and contagious) but asymptomatic. These patients are considered "colonized" and are at higher risk of developing CDI.

Research on CDI prevention practices has evolved and expanded over the last decade. The research summarized in this section reviews not only new knowledge, but also new technologies and policies now in widespread use. For example, electronic health records (EHRs) are valuable for antimicrobial stewardship efforts and CDI surveillance. Research on no-touch decontamination technology has grown in the last 10 years, as has understanding of CDI transmission pathways. Testing methods have also evolved, with Food and Drug Administration (FDA) approval of nucleic acid amplification tests (NAATs) in 2009. There are increased mandates for surveillance of CDI and the standard interim CDI case definitions that the CDC published in 2007 have been revised in recent years. Facilities have implemented new automated surveillance systems, and CDI data collection at the national level is now standardized, with the advent of the National Healthcare Safety Network's (NHSN's) LabID Event reporting in 2013.

Potential for harm

CDI is among the most common HAIs, representing roughly 12 percent of all HAIs.[45] Approximately half a million incident clinical infections occur (with more than 100,000 in U.S. nursing homes) per year in the United States, with around 30,000 deaths per year as a result of the pathogen. The financial cost of CDI is also high; in recent years, CDI has resulted in about $5 billion a year in healthcare costs. Costs attributable to primary and recurrent CDI are $24,205 and $10,580 per case, respectively.[46] CDI colonization is also a concern, and around 10 percent of admitted hospital patients were colonized with C. difficile.

CDI incidence nearly tripled in the first decade of the 21st century, and data from 2010 to 2016 showed CDI rates plateauing. However, after falling short of 2013 reduction goals, the Department of Health and Human Services set a target reduction of 30 percent in hospital-onset CDI from 2015 to 2020. Healthcare-associated CDI has been decreasing slightly, while community-associated (CA) CDI is stable or increasing slightly; according to CDC estimates, in 2015, almost half of CDI cases were CA.

The clinical severity of the infection has also evolved. Increasingly virulent strains were a concern roughly 10 years ago. However, a 10-year study of a sample of inpatient data found CDI-related mortality rates declined from 2005 to 2014.[47] Other CDI incidence outcomes, including rates of recurrent CDI, have increased. It is notable that healthcare-associated CDI incidence trends differ based on setting, with a greater decline seen in nursing homes versus hospitals and other healthcare facilities.

Reimbursement policies have increasingly mandated and reinforced the reduction of CDI. CDI LabID Event reporting began in January 2013 for all acute care hospitals facility-wide using the NHSN. The Centers for Medicare & Medicaid Services (CMS) Inpatient Quality Reporting program's CDI reporting requirements became mandatory as of January 1, 2013. Since 2017, CDI rates are among the hospital- acquired complications CMS uses to penalize the lowest performing hospitals. Many States also now mandate CDI data submission by hospitals to NHSN as part of State HAI public reporting programs. In the future, participation in surveillance reporting will increase and include a broader spectrum of settings. For example, data from a larger group of LTCFs will be used to establish national benchmarks and track achievement of prevention goals.

Antimicrobial stewardship

This section will briefly review the foundational elements of antimicrobial stewardship programs (ASPs) as recommended by the CDC and how antimicrobial stewardship is believed to work as a safety practice for preventing CDI. It will examine the evidence for the estimated effect of ASPs on CDI incidence rates and then provide a summary of common ASP components.

ASPs are intended to limit and optimize antimicrobial prescribing, reduce the evolution of antibiotic-resistant bacteria, and improve patient outcomes. To meet these goals, the CDC provides a basic framework of recommendations for hospital settings, summarized here:[48]

- Leadership Commitment: Dedicating necessary human, financial, and information technology resources.
- Accountability: Appointing a single leader responsible for program outcomes. Experience with successful programs shows that a physician leader is effective.
- Drug Expertise: Appointing a single pharmacist leader responsible for working to improve antibiotic use.
- Action: Implementing at least one recommended action, such as systemic evaluation of ongoing treatment needs after a set period of initial treatment (e.g., "antibiotic time out" after 48 hours).
- Tracking: Monitoring antibiotic prescribing and resistance patterns.
- Reporting: Regularly reporting information on antibiotic use and resistance to doctors, nurses, and relevant staff.
- Education: Educating clinicians about resistance and optimal prescribing.

These elements are foundational and meant to complement additional ASP guidelines. The CDC notes that no template exists for an ASP, and ASPs can be effective in a variety of settings and under a diverseset of conditions. While the ASPs studied in the papers selected for this report included these foundational elements to varying degrees, they take many different forms based primarily on a particular facility's resources and needs. Frequently, the ASPs are developed and executed by a multidisciplinary team with medical, pharmaceutical, and/or microbiological expertise.

ASPs require tracking and reporting of data (at minimum quantifying antimicrobial use and CDI rates), as well as staff education and outreach. The "Action" element is operationalized through different strategies, the most common of which are patient case reviews, audits of antimicrobial use, restrictions on high-risk antimicrobials, and provider education. The Infectious Diseases Society of America and Society for Healthcare Epidemiology of America (IDSA/SHEA) guidelines recommend minimizing the frequency and duration of high-risk antimicrobials and using local epidemiology to determine which antimicrobials to address in an ASP. The guidelines further state that ASPs should consider reducing/restricting the use of drugs including fluoroquinolones, clindamycin, and cephalosporins.

Antimicrobial stewardship as a PSP

Antimicrobial exposure is widely considered one of the most significant and modifiable risk factors for CDI. In the last two decades, at the population level, increasing rates of CDI have been linked to increases in antimicrobial prescribing, particularly in older patients.[49] Patients receiving, or having recently received, antimicrobial therapy are more susceptible to colonization or infection with pathogenic bacteria such as *C. difficile* because antimicrobials alter gastrointestinal tract flora, destroying the bacteria that help to protect against *C. difficile*.

The length and type of regimen also impacts CDI risk. Several broad-spectrum antimicrobials have been most strongly linked to CDI, and certain outbreaks appear to be associated with heavy prescribing of particular antimicrobials. Therefore, many CDI ASPs are designed to reduce the use of particular "high- risk" antimicrobials. The CDC found that people receiving high-risk antimicrobials had a three times higher risk of CDI than did people with low-risk or no antibiotic use.[50]

There is increasing urgency about reducing overreliance on antimicrobials). The CDC estimates that between 30 and 50 percent of antimicrobial prescriptions are clinically inappropriate.[51]

Other countries have similar efforts, and a number of resources are designed to help facilities implement ASPs.

To implement changes in prescribing practices, ASPs use various strategies or interventions, which are typically grouped into the following categories: formulary restrictions, audit and feedback, and provider education. There is some research about outcomes associated with each individual strategy, but usually ASPs use more than one of the above interventions, making it difficult to assess each approach individually. Approaches that are "restrictive," (i.e., restrict high-risk antimicrobials) tend to be more effective than the "persuasive" strategies (i.e., audit and feedback, education, guidelines). There is no consensus on which interventions are most effective, and it is likely that the most effective approach may differ in different settings; effective programs are dynamic and can be adapted to facility needs.

Target antimicrobials

An important first step in formulary restriction is determining which antimicrobials to target for restriction. In addition to reducing the high-risk antimicrobials outlined in current guidelines, facilities may use data on regional and facility associations between CDI and antimicrobials. In one example, an ASP team examined temporal associations between antimicrobial use and CDI cases in their facility to determine which antimicrobials to target for restriction.

Once target antimicrobials have been identified, ASPs may use strategies such as preauthorization requirements and removing access to the target antimicrobials. In a systematic review, Feazel et al. (2014) reported that interventions that included restricting high-risk antimicrobials (e.g., preauthorization requirements, restrictions on certain antibiotics except in unusual circumstances) were associated with the greatest reductions in CDI rates.[52]

Audit and feedback include case reviews of patients receiving antimicrobial therapy, often involving a multidisciplinary team (e.g., prescribers, pharmacists, infectious disease experts, administrators) and feedback to providers, as well as audits of targeted antibiotics and other clinical measures both before and/or after treating the patient. Feedback to prescribers may include advice about switching to alternative antimicrobial agents (e.g., broad to narrow spectrum), discontinuation of antimicrobial treatment, shortened duration of microbial dose, higher or lower dose, and switch from intravenous to oral antibiotics. The latter recommendation is based on the idea that an earlier switch to oral therapy allows faster discharge from the hospital, thereby reducing exposure to CDI and drug-resistant organisms.

ASPs with an audit and feedback component are widely recommended antimicrobial stewardship practices; however, ASPs based solely on an audit and feedback program showed no statistically significant reductions in CDI. One benefit of audit and feedback is that the practice itself educates prescribers and other healthcare staff. In most studies, audit and feedback are accompanied by a staff education component, making it difficult to find associations between audit and feedback alone and CDI rates.

Staff education

Researchers suggest that education is important to provide context and convince physicians and other staff to participate in antimicrobial stewardship activities. Some rehabilitation physicians may be aware of the problem of antimicrobial resistance but unaware of local resistance patterns. Education programs typically include information about antimicrobial resistance, local and facility antibiogram data, treatment guidelines, and/or CDI- specific education. Educational methods can include the use of emails, pocket cards, presentations, and trainings.

In an attempt to isolate the CDI associations of an educational program (as part of a multicomponent strategy), Shea et al. (2017) assessed results associated with a 3-month education campaign, then, separately, the results following a subsequent 12 months of a fluoroquinolone restriction policy.[53] The shorter education component appeared to have a significant impact, which was enhanced by the restriction policy. Compared with pre-ASP, the four hospitals experienced 48 percent and 88 percent average reductions in fluoroquinolone utilization (days of therapy per 1,000 patient days) after education and restriction, respectively. CDI rates decreased significantly from 4.0 cases/10,000 patient days pre-ASP to 3.43 cases/10,000 patient days following staff education, and to 2.2 cases/10,000 patient days following restriction.

Unanticipated outcomes of ASPs

One potential consideration with ASPs is that they may encourage the use of (untargeted) broad- spectrum agents and/or alternative "lower-risk" antimicrobials, which, in turn, may lead to increased resistance to the unrestricted drugs. This has been called the "squeezing the balloon" phenomenon, wherein restriction policies for use of one set of drugs leads to increased use of unrestricted alternatives, which leads to resistance. This practice runs counter to the goal of decreasing antimicrobial selection pressure.

While many studies find overall reductions in antibiotic use up to 30 percent, or no significant change in overall antimicrobial use, some researchers reported increases in nontargeted antimicrobials. For example, Dancer and colleagues (2013) found that while targeted antimicrobials decreased during the ASP period, use of empiric amoxicillin and gentamicin increased, and resistance to these antimicrobials increased.[54]

One of the positive outcomes of a CDI-targeted ASP can be lower rates of MRSA (methicillin-resistant Staphylococcus aureus), ESBL (extended-spectrum beta-lactamases)-producing coliform infections, and other MDROs (multidrug-resistant organisms). For example, while the primary reason for the antimicrobial restrictions and revised prescribing guidelines in the ASP studied by Dancer et al. (2013) was to decrease CDI rates at the hospital, the researchers also found decreases in ESBL-producing coliforms following the ASP an 8.21 percent reduction. During the following 3 years, both ESBL-producing coliform infections and MRSA declined.

One additional benefit (or perhaps less identified outcome of an ASP) can be an increase in the accuracy of patient diagnoses following audit and feedback interventions. Talpaert et al. (2011) found that, out of 386 interventions by the ASP team, on 75 occasions the clinicians changed the patient's diagnosis.[55]

ASPs require resources, and sometimes creative mechanisms to address resource gaps. Researchers have noted challenges with staffing limitations (when additional staff were not hired for the ASP) and a need for technical resources to track antimicrobial use. In addition, the lack of EHRs in many LTCFs can make it hard to track the exact indication for antimicrobial use. However, even with limited means, antimicrobial stewardship can produce meaningful benefits. For example, Yam et al. (2012) described the challenges of resource constraints in a small rural hospital.[56] The ASP team decided to use scheduled and as-needed consultations with a remote infectious disease specialist physician. After the ASP worked with the remote specialist for 13 months, the researchers found nosocomial CDI decreased from an average of 5.5 cases per 10,000 patient days to an average of 1.6 cases per 10,000 patient days, and antibiotic purchase costs decreased nearly 50 percent.

- The CDC provides recommendations for resource-limited settings, which include:
- Using nontraditional staff types to lead the ASP (e.g., infection control nurses, clinical microbiologists, or pharmacists without infectious disease training);
- Using telehealth for advising on prescribing decisions;
- Identifying a single priority hospital unit (e.g., ICU) in which to implement an ASP; or
- Choosing and implementing a single prescribing practice (e.g., reviewing the need for antibiotics after 48 hours, or improving adherence to guidelines for empiric treatment for CA pneumonia or sepsis).

Resistance on the part of providers is a major barrier to ASP implementation that is described in the literature; conversely, a facilitator to implementation is a good relationship between the ASP team and prescribers. Educating physicians and providing proof of ASP safety and efficacy are essential to garnering support. Dancer et al. (2013) found that gaining support for their ASP was challenging at the outset, especially when ASP recommendations for prescribing conflicted with previously published guidelines for a specific infection. For example, gastroenterologists initially refused to curtail ciprofloxacin prescribing for spontaneous bacterial peritonitis. After being educated about the microbiological etiology of the infection, the gastroenterologists were persuaded to change prescribing practices.

Hand hygiene

In the 2017 clinical practice guidelines for preventing C. difficile, IDSA states that HCWs "must" use gloves while caring for CDI patients, including when entering a room with a CDI patient.[57] In CDI outbreaks or hyperendemic settings (periods of persistently high levels of CDI), the guidelines include performing hand hygiene with soap and water before and after caring for a patient with CDI and after removing gloves. When working with CDI patients in routine or endemic situations, the guidelines recommend washing hands with soap and water or using alcohol-based hand rubs (ABHRs) for hand hygiene after removing gloves. While ABHRs are the preferred means of disinfecting hands for most pathogens, alcohol is not active against C. difficile spores, and it is believed that the most efficacious way to eliminate *C. difficile* is via the mechanical action of handwashing. Washing hands with soap and water is recommended after any contact with feces.

The World Health Organization campaign, "My Five Moments for Hand Hygiene," promotes hand hygiene at the following times:

- Before touching a patient
- Before clean/aseptic procedures
- After body fluid exposure/risk
- After touching a patient
- After touching patient surroundings

Use of proper handwashing technique is important for *C. difficile* spore removal. When handwashing is indicated, guidelines recommend vigorous and thorough washing of all surfaces for at least15 seconds. The entire process from start to finish should take between 40 and 60 seconds. This technique has been tested against unstructured and alternative techniques and found to be most effective at removing *C. difficile* spores.

General CDC recommendations (for all HAIs) call for antibacterial soap over plain soap. However, in experimental studies, some researchers have found that plain soap is more effective for removing C. difficile spores.[58] This is one of several unresolved issues in hand hygiene for *C. difficile.*

The CDC defines hand hygiene as a general term that applies to either handwashing, antiseptic hand wash, antiseptic hand rub, or surgical hand antisepsis. As such, glove use was not included in most of the reviewed studies. However, *C. difficile* hand hygiene recommendations strongly recommend the use of gloves. One study found that universal glove use (with emollients for skin care) at 78 percent compliance was more effective than standard contact precautions (use of gowns and gloves; 67% compliance) to avoid *C. difficile* transmission.[59]

Health care workers (HCWs) should conduct hand hygiene before and after wearing gloves. Appropriate technique helps prevent potential hand contamination when removing gloves. Gloves should not be reused on more than one patient.

Multiple studies have found *C. difficile* contamination on healthcare workers' hands and several studies have linked cases of CDI and CDI outbreaks to HCW transmission. Similarly, inadequate hand hygiene has been linked to higher incidence of CDI. A study that looked specifically at HCW hand contamination after contact with CDI patients found that 24% of HCW hands were contaminated with CDI (even when gloves were used in 356/386 of patient contacts).[60] In addition, contact without the use of gloves was independently associated with hand contamination (adjusted OR, 6.26; 95% CI, 1.27 to 30.78).

Due to concern about HAI rates and poor HCW hand hygiene compliance, hand hygiene (including use of ABHRs) has been heavily promoted over the last two decades. But one systematic review found median hand hygiene compliance across 96 studies in a variety of healthcare settings was only 40%, and hand hygiene rates are potentially even lower at LTCFs.[61]

Patient hand hygiene

In the past decade, patient hand hygiene has received increasing attention as a potential major source of *C. difficile* transmission in healthcare settings. Patients colonized with *C. difficile* often go undetected and may transmit *C. difficile* to HCWs' hands directly, or indirectly through contaminated surfaces in the healthcare environment. Patient mobility, dexterity, and cognitive limitations can be barriers to patient hand hygiene. One study found patient hand hygiene compliance rates as low as 10%.[62]

Implementation

Interventions to increase hand hygiene compliance in healthcare settings fall into five general intervention types:

- Education
- Facility design (installation of sinks and ABHRs)
- Unit-level protocols and procedures
- Hospital-wide programs
- Multimodal interventions

It is recommended that hand hygiene education be interactive and engaging and that interventions be tailored to the institution's unique needs. Researchers have assessed barriers to hand hygiene and report that hand hygiene interventions should be tailored to the particular classification/ role of staff and that context and staff needs should be taken into account when designing hand hygiene interventions.

An interactive strategy to assist HCWs in improving glove and gown removal technique includes the use of fluorescent lotion. In the training described by Tomas et al. (2015), fluorescent lotions were used to help HCWs learn proper glove and gown removal to minimize hand contamination.[63] The fluorescent lotion provides immediate visual feedback on contaminated sites. A similar strategy includes the use of nonpathogenic RNA beads that fluoresce under ultraviolet (UV) light to help track contamination during removal of personal protective equipment. This practice can help HCWs see that glove use does not preclude the need for hand hygiene.

The design of the healthcare environment can affect hand hygiene compliance. Some researchers suggest a human factors engineering approach that calls for abundant, convenient, and available sinks, handwashing products, and ABHRs to improve compliance. Several researchers found that longer distances to sinks, and sink visibility, were related to HCW handwashing compliance.

Key findings

- Gloves and handwashing with soap and water are the recommended hand hygiene practices for *C. difficile* prevention.
- Multiple experimental studies show ABHRs are not effective in eliminating *C. difficile* spores.
- Studies are needed that measure *C. difficile*-targeted hand hygiene initiatives, as well as financial outcomes, and hand hygiene programs in nonhospital settings.
- Important contextual factors for CDI/hand hygiene include sink location, visibility, and accessibility.
- Future directions for hand hygiene programs include patient hand hygiene, studies on glove compliance, electronic monitoring, and sustainable interventions.

Infections due to other multidrug-resistant organisms

Multidrug-resistant organisms (MDROs) are microorganisms, mainly bacteria, that are resistant to one or more classes of antimicrobial agents. These include methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant Enterococci species (VRE), carbapenemase-producing Enterobacteriacea, and Gram-negative bacteria that produce extended spectrum beta-lactamases (ESBLs). These last two types of pathogens produce chemicals that allow them to resist the effect of certain antimicrobials, and this adaptation is easily passed between different species.

Other species of note include MDR *Escherichia coli* and *Klebsiella pneumoniae*, *Acinetobacter baumannii* (abbreviated AB; some strains are resistant to all antimicrobial agents), and organisms such as *Stenotrophomonas maltophilia* that are intrinsically resistant to the broadest-spectrum antimicrobial agents. MDROs' resistances limit treatment options for patients, making infection critical to preventing further harms.

Background

The World Health Organization (WHO) now recognizes that MDROs are a growing threat in every geographic region of the world. Drug-resistant bacteria pose a significant public health risk both domestically and abroad due to their ability to colonize individuals without causing symptoms, their endurance in the environment, and the clinical threat they pose. The growing presence of resistant microbes is of particular concern for vulnerable patients, such as those who have received organ transplantation, those with cancer, preterm infants, and immune-suppressed and other medically vulnerable individuals.

With treatment complicated by the limited availability of antimicrobials to treat these infections, MDROs are responsible for approximately 23,000 deaths annually from antibiotic-resistant pathogens in the United States alone.64 The CDC states that 10% of individuals screened in healthcare facilities are asymptomatic carriers for a transmissible, "hard-to-treat" microorganism.[65]

Drug-resistant organisms are becoming increasingly present in all settings and geographic areas. Carbapenem resistance increased in five European countries from 2008 to 2011. In the United States, infections caused by multidrug-resistant, Gram-negative bacteria have increased over the past decade, and one out of five hospitals reporting invasive infections implicated a carbapenem-resistant K. pneumoniae, one of the most common MDROs. While rates of hospital-onset, MRSA-related bacteremia in the United States have declined, community-onset MRSA-related bacteremia has increased in recent years.

The patient safety practices in this report have universal application for reducing the burden of colonization and infection. When differences are significant (e.g., Enterococci in the digestive tract vs. S. aureus on patient skin), we make a note in the findings. The large benefit of these practices, however, comes from this universality: whether the organism is an extremely drug resistant A. baumannii or methicillin-susceptible S. aureus, infection prevention reduces risks and prevents patient harms. Communicating patients' MDRO status allows facilities to take appropriate infection prevention precautions from the start of the patient encounter.

PSP: Chlorhexidine Bathing To Control MDROs

Chlorhexidine solutions have broad antimicrobial activity and are already commonly in use as topical disinfectants and antiseptics as part of recommended strategies for MDRO control and infection prevention. Either universal or targeted chlorhexidine bathing can complement other infection control methods of screening, isolation, and eradication.

This section examines specific efficacy of chlorhexidine to prevent different infections (by organism, by type of infection), the mode and frequency of successful chlorhexidine bathing for disease prevention, and considerations for or unintended consequences of general chlorhexidine use.

"Chlorhexidine bathing" is defined as application of chlorhexidine to the skin or oropharyngeal surfaces to promote decolonization and to prevent infection. As described below, oropharyngeal surfaces represent a reservoir for MDROs in mechanically ventilated patients who cannot perform their own oral care. Since chlorhexidine bathing is recommended for patients at high risk for MDRO-related infections

- generally intensive-care patients, many of whom may be mechanically-ventilated as part of their care
- we include oral care as part of a chlorhexidine bathing routine.

MRSA

Evidence suggests that chlorhexidine bathing in the hospital setting reduces MRSA acquisition and carriage but may not always result in fewer MRSA infections. Three systematic reviews found evidence that chlorhexidine bathing alone reduces MRSA acquisition and carriage. This finding is supported by five strong studies (four experimental, one quasi-experimental) that also found chlorhexidine bathing reduced MRSA carriage and acquisition. While most of these studies found that bathing also reduced MRSA infections, some studies found no significant reduction in infections.

One prospective cohort study found no reduction in MRSA colonization rates, specifically, but did find a significant reduction in the rates of infections caused by all MDROs (measured in aggregate, not by specific MDRO). Interpreting these results is made more difficult by the fact that chlorhexidine bathing is recommended as part of a multicomponent strategy that includes nasal mupirocin and, in a few studies, oral antibiotics, as described in general MDRO and MRSA control guidelines.

In long-term care facilities, a thorough decolonization protocol that includes chlorhexidine bathing can reduce MRSA colonization without the need for patient isolation. This is an important finding for implementation, because extended patient isolation and gown and glove use may not be feasible or desirable in long- term or residential care settings.

VRE

Several studies found evidence that chlorhexidine can reduce VRE acquisition and colonization. One rigorous, multicenter study found that chlorhexidine bathing can reduce VRE acquisition. Three systematic reviews found that chlorhexidine can reduce VRE carriage in hospital patients. Finally, two quasi-experimental studies found reduced VRE colonization among patients who were bathed daily with chlorhexidine.

CRE

Few studies directly addressed chlorhexidine effects on CRE specifically (a number focused on the larger category of MDR-GNB). Of those that did, two observational cohort studies found that chlorhexidine bathing could reduce CRE colonization.

HAIs

Many studies examined the effect of chlorhexidine bathing on rates of various HAIs, such as catheter- associated urinary tract infection (CAUTI), ventilator-associated pneumonia (VAP) g, and central line- associated blood stream infection (CLABSI). Based on the studies included, chlorhexidine bathing is most effective at reducing colonization by and HAIs from Gram-positive MDROs in patients who have a break in the skin due to a needed medical device (e.g., central line).

One review and several studies, including two large studies with more than 10,000 patients and 400,000 patients, respectively, have found evidence that chlorhexidine bathing can reduce the risk of HAIs, especially in intensive care units. One trial found universal decolonization involving daily chlorhexidine bathing throughout the patient's entire ICU stay and twice-daily intranasal mupirocin for 5 days was more effective than targeted decolonization or screening and isolation in reducing MRSA-positive clinical cultures and all-cause bloodstream infections.

Most studies of chlorhexidine for HAI prevention focused on BSIs, but a few looked at VAP and SSIs. An observation study (found no reduction in intubation-related pneumonia, nor in UTIs, although overall infections and catheter-related infections were significantly lower.[66]

Although chlorhexidine is routinely used for preoperative antisepsis in surgical settings, no studies suggest that chlorhexidine bathing reduced SSIs (although some observe a reduction in SSIs among CRE-colonized patients in their study).

An important limitation applies to all these studies: because of other HAI prevention initiatives, the absolute number of HAIs is, in some cases, very low. The number needed to treat with chlorhexidine bathing in order to significantly reduce HAIs may be, in some cases, larger than the number of patients enrolled in studies. This finding suggests that chlorhexidine bathing has limited benefit for HAI reduction in settings where HAIs are already well controlled by other means.

Application

Chlorhexidine bathing, as described in the literature, covers a range in terms of concentration used, mode of application, and frequency. Of those studies that described the frequency of application, almost all described daily chlorhexidine bathing, with a smaller number using multiple applications per day (4 out of 24, of which one was an oropharyngeal-only application of chlorhexidine).

In terms of concentration, the vast majority of reviews and studies used a 2% chlorhexidine gluconate solution (either in prepackaged wipes or applied using a soaked washcloth). For otherwise healthy patients outside a hospital setting, daily bathing with 2% chlorhexidine cloths is ineffective in reducing soft skin and tissue infection. Chlorhexidine's effectiveness includes prolonged residual disinfection, so it is important not to rinse after use.

The most common adverse effect in the literature was skin irritation. When use of chlorhexidine wipes was discontinued, pruritus stopped. Oral mucosa lesions were observed in 9.8% percent of the 8,665 mechanically ventilated patients in Wittekamp and colleagues' chlorhexidine mouthwash study.[67] More serious adverse effects can occur with exposure to sensitive areas (eyes, esophagus, intestinal lining, inner ear). Severe anaphylaxis is possible but rare.

Evaluations of Chlorhexidine Resistance

The most important unintended consequence of the wide use of chlorhexidine is the development of resistance to chlorhexidine and other biocides.

None of the MDROs in the studies in this review showed biocide resistance at the concentrations typically used for chlorhexidine bathing; the in vitro studies compared survivability of resistant MDROs in low concentrations of chlorhexidine. An equal number of studies supported or refuted the hypothesis that chlorhexidine bathing increases the prevalence of resistance genes in hospitals; however, many of these studies looked at isolates from a single hospital and may have limited generalizability. Regardless of changes in prevalence, these authors hypothesize that overdiluted concentrations or residual chlorhexidine may be selecting for resistant organisms (either resistant clones/strains or organisms less susceptible to chlorhexidine) and should be monitored for clinical impact.

Clinical Implications

The clinical impact of chlorhexidine resistance genes is unclear. One in vitro study of MRSA isolates in a U.S. hospital found that MRSA strains showed more resistance to chlorhexidine than methicillin-susceptible strains. Other studies found more chlorhexidine resistance in VRE than in vancomycin-susceptible Enteroccoci strains in isolates from Danish hospitals. Some evidence suggests that chlorhexidine bathing can favor chlorhexidine-resistant MDROs (particularly MDR-GNB) by eliminating the "competition" from chlorhexidine-susceptible MDROs.

Importantly, no studies suggest that chlorhexidine bathing was ineffective due to resistance; at the concentrations typically used (1-4%), chlorhexidine still kills even the most resistant organisms. However, overdiluted solutions may fail to kill organisms as intended and create unwanted transmission and infection, especially in cases where biofilms have formed.

Some alternatives to chlorhexidine, such as triclosan and hydrogen peroxide, have their own risk of resistance selection. Cationic compounds show promising effectiveness against MDROs, but it will be some time before these products are commercially available.

Implementation

As described above, the most common frequency of chlorhexidine bathing is daily, and the most common application is a 2% chlorhexidine gluconate solution, either in prepackaged wipes or in soaked washcloths. One important aspect of chlorhexidine use is to allow long-term contact with the skin, with a recommended contact time of at least 5 minutes. No-rinse applications can further take advantage of chlorhexidine's persistent antimicrobial effects on the skin.

Chlorhexidine can be successfully used for MRSA decontamination, when combined with mupirocin and active surveillance. However, the effectiveness of decolonization for otherwise healthy populations is unclear. While some studies find successful reductions in skin and soft tissue infections in healthy populations by instituting daily bathing with 2% chlorhexidine-impregnated clothes, others did not find benefits to introducing chlorhexidine in a non-critical care hospital setting.

In general, daily chlorhexidine bathing is a low-cost strategy that is well received by staff. Chlorhexidine bathing also has the advantage of being easy and quick to implement, although compliance can wane over time. Good leadership support for an infection control program can increase regular use of chlorhexidine bathing, and when facilities implement chlorhexidine bathing, leadership support for infection preventionprograms can help sustain compliance with bathing over time.

Key Findings

- The strongest evidence supports using chlorhexidine bathing to reduce colonization and infection, particularly by multidrug—resistant Gram-positive bacteria (MDR-GPB) such as MRSA and VRE, and for healthcare-associated infections (HAIs) related tomedical devices that create a break in the skin (e.g., central lines).
- Less evidence is available to support chlorhexidine bathing for preventing infection from MDR Gram-negative bacteria (MDR-GNB), such as carbapenem-resistant Enterobacteriaceae (CRE), and for other types of HAIs.
- As an intervention, chlorhexidine is low cost to implement (especially if routine bathing is already in place) and generally well received by staff, but compliance with bathing can wane over time.
- While the literature has not described any clinical effects of chlorhexidine resistance, this practice should continue to be monitored.

Active Surveillance for MDROs

"Active surveillance" is a broad practice that encompasses many activities, including sample collection, laboratory testing, data collection, data analysis, and reporting and feedback. Active surveillance helps prevent the spread of infection by identifying when an MDRO enters a healthcare facility and quickly triggering infection control measures. Active surveillance can also help with diagnosis and appropriate treatment of infections and antibiotic stewardship by generating data that can be used to create a local profile of antibiotic susceptibility or antibiogram.

Epidemiologically, genotyping of active surveillance samples can help identify potential modes of transmission or assess need for patient bathing/deeper environmental cleaning by identifying related organisms from multiple sample sites. These genotyping data can also be used to identify whether the MDROs identified in screening are endemic to the environment or are imported by asymptomatic carriers. However, this practice requires access to labs with the capacity to do quick-turnaround, real- time genotyping.

Integration of active surveillance programs into electronic medical records can help automate identification and analysis but requires facilities with those capacities or access to them. However, generating larger, regional and even global surveillance systems allows individual facilities to identify risk factors for incoming patients (for example, knowing what areas of the world have high prevalence of certain MDROs).

Many resource challenges arise in creating sophisticated laboratory and data integration systems that can identify, genotype, and share information on MDROs. At the same time, investing in these systems benefits other infection control practices by generating the data that allow facilities to take a risk-based approach to screening, isolation, and contact precautions, which represent an opportunity for cost saving. Finally, facilities must make decisions about when to stop active surveillance, balancing the costs of an active surveillance program against the possibilities of failed eradication and recolonization.

Active surveillance for MDROs is necessary because routine surveillance of clinical samples will undercount colonized or infected patients. The proportion of clinically evident cases also varies by organism and susceptibility of the patient population, which means many asymptomatic carriers will go unnoticed without active surveillance. In addition, an accurate screening process will reduce the number of patients on isolation or contact precautions unnecessarily. In an outbreak of an MDRO in an otherwise low-prevalence setting, active surveillance is needed to verify that the outbreak has been successfully contained. It is recommend that surveillance always be paired with other infection prevention practices.

Screening Methods for Detecting MDROs

Although screening is widely used, findings are mixed as to the correct screening method (patient sites, type of swabs used), frequency, target population, and culturing of samples. The sensitivity and specificity of a sample collection site or type varies by type of MDRO.

Given the costs associated with active surveillance and subsequent patient isolation, universal surveillance is recommended in facilities where the incidence of MDROs is moderate to high and for patients for whom the rate of conversion from colonization to infection is high (e.g., transplant patients). In universal surveillance, skin, blood, and respiratory samples perform better at initially identifying the presence of an MDRO than did urine samples. The CDC (2019) offers guidelines for surveillance based on different categories of organisms and resistance mechanisms, with a recommended approach for each.[68]

General MDR-GNB: No consensus exists on frequency of screening or timing of screening for MDR-GNB. One review showed that screening during admission with weekly followup prevented the spread of MDR-*A. baumanii*. But a similar program for MDR-*K. pneumoniae* was not successful. In epidemic settings, targeted screening on admission for high-risk patients is recommended. Screening can also be used to reinforce other prevention practices in the outbreak response, such as hand hygiene.

In the endemic setting, active surveillance should be used as an additional measure to control the spread of MDR-GNB between facilities or units. Surveillance data from endemic settings should be used to build risk assessment protocols and implementtargeted screening policies that will catch MDR-GNB carried by transferred patients without adding unnecessary costs or burden.

As far as sampling sites, rectal swabs, urine, or respiratory secretions are sufficient for almost all MDR-GNB, with rectal swabs being the most sensitive and groin being most specific. However, sensitivity of screening is low (29%) even when six body sites are included. Although rapid polymerase chain reaction-based methods to identify MDR-GNB are in development, culture-based tests remain the standard.

Once an MDR-GNB pathogen is identified, weekly screening is recommended until no cases of colonization/infection or cross-transmission are observed. Several outbreak responses have noted that MDR-GNB pathogens, particularly MDR-AB, produce significant environmental contamination due to their method of shedding (shed skin cells, stool, and/or urine). However, the mean colonization time for MDR-GNB is 144 days, representing a significant length of time. The efficacy of screening is linked to the level of compliance, so screening must be maintained over time.

Methicillin-resistant Staphylococcus aureus (MRSA): Given the increasingly endemic nature of MRSA in both healthcare and community settings, questions have emerged about the clinical value of screening for MRSA, especially among asymptomatic carriers. If conducting screening for MRSA, nasal screening is most sensitive

MRSA screening may be a useful tool for identifying colonization of other, nonendemic MDROs. Evidence supports some association between MRSA status at admission and later discovery of MDRO colonization. In facilities where universal MRSA screening is already in place, a positive result may be considered a risk factor for other MDROs. By knowing risk factors associated with colonization by MDROs other than MRSA, hospitals and other facilities can develop risk-based testing approaches for screening on admission, reducing costs in time and materials.

Vancomycin-resistant Enterococci (VRE): Active surveillance for VRE can help detect asymptomatic carriers, but the clinical benefit of this strategy is unclear and methods for VRE surveillance can vary widely in practice. Active surveillance helps detect asymptomatic VRE colonization in patients with C. difficile infection (CDI) in facilities with a high VRE prevalence, given high correlation between colonization with the two organisms. More than 50 percent of patients with CDI were also colonized with VRE. Despite this finding, it is not clear whether surveillance for asymptomatic VRE carriers reduces VRE- related infections.

Carbapenem-resistant/carbapenemase producing Enterobacteriaceae (CRE/CPE):

Although the global prevalence of CRE/CPE is increasing, not all regions or all facilities in a region share the same risk for CRE outbreaks. Active surveillance following identification of CRE can reveal additional asymptomatic cases. Rescreening of clinical samples collected for other testing is one way to efficiently screen patients who have risk factors for multiple MDROs and identify asymptomatic carriers.

In light of no clear evidence for or against universal screening for CRE, active surveillance on admission for patients in any of the following elevated risk groups is recommended:

- Patients transferred from a healthcare facility in any foreign country (in light of a lack of data on global CRE prevalence
- Patients transferred from acute or long-term care facilities with known high CRE prevalence
- Patients previously colonized or infected with CRE
- Patients who have had close contact with a person with CRE.

Any surveillance must have clear definitions to avoid under- or over-reporting of CRE cases.

Environmental Sampling for MDRO Surveillance

Active surveillance of the environment, in addition to patients, combined with monitoring staff's adherence to infection control practices, can identify the transmission patterns and expose areas for improvement. Environmental sampling as part of active surveillance can be used to identify areas in need of intensive cleaning or where cleaning has been missed. Environmental surveillance may serve as an indicator of MDRO carriers, at least in the case of MDR-AB, where the organism is consistently shed by patients.

Genotyping MDRO Cultures

Genotypic testing can help determine whether MRDOs identified in active surveillance are horizontally transmitted between patients, coming from a common environmental reservoir, or are imported from other facilities.

Negative unintended consequences

Active surveillance is used to identify patients to be placed on contact precautions, which reduce transmission but may have unintended adverse effects on the patient. Contact precautions have been associated with less contact from healthcare workers, delays in care, adverse events (non-infection- associated), increased symptoms of depression and anxiety, and decreased patient satisfaction with care. Rapid-result genetic testing can reduce any potential adverse effects of contact isolation by limiting the time spent in preemptive isolation pendingscreening results.

A potential negative consequence of public education about and coverage of outbreaks could be increased community anxiety. When sharing information on outbreaks and infection prevention responses with patients and families, one must convey the importance of preventing transmission and managing patients' understanding of their individual morbidity and mortality risk. Publications on techniques used to control the outbreak in a facility as well as media coverage of the outbreak, for example, could be shared.

Barriers and Facilitators

Adding weekly dissemination of the results of active surveillance (MDRO rates, location of acquisition) can be key to successfully controlling MDROs. Although other components (active surveillance, patient isolation) may be in place already automated systems could support enforcement of contact precautions and save considerable infection preventionist time. Horizontal transmission of MDRO strains may not need universal active surveillance, but MDRO acquisition or infection between facilities warrants communication to identify patients at elevated risk. Coordination with regional and national public health agencies can help with interfacility transmission by coordinating notification and infection prevention efforts across all facilities.

Investing in active surveillance can require expenditures for laboratory and computer resources, but these investments can help reduce the cost of other infection prevention efforts. If a facility cannot absorb the costs of running a laboratory, partnering with public health agencies for surveillance may be an option. Faster results can be available using molecular testing methods such as polymerase-chain reaction, but these tests can be costly, have limited specificity in some cases, and are not available in all facilities.

Surveillance and isolation precautions do not require specific patient consent, however education and clear communication about the need for and impact of active surveillance on patients are critical. In addition, the financial burden of active surveillance should be assumed by the facility, not the patient.

Key Findings

Targeted active surveillance performs as well as universal active surveillance for many MDROs and uses fewer resources. However, in places where universal active surveillance is already in place, screening for other MRDOs using the same sample may be cost- effective, as patients colonized with an MDRO share risk factors for others.

Some consensus exists for screening high-risk patients (those with a history of MDROs or risk factors associated with MDRO colonization/ infection) on admission, but any screening approach will require compliance with infection prevention protocols when a patient's culture result is positive.

Surveillance may improve compliance with other PSPs when it is part of a multicomponent intervention, but more research is needed on the mechanisms and circumstances of this association, as it can be confounded by the co-implementation of other, bundled practices.

Environmental cleaning and decontamination

The CDC defines the practice of cleaning in the healthcare environment as the removal of visible soil (e.g., organic and inorganic material) from objects and surfaces. The CDC defines disinfection as the elimination of many or all pathogenic microorganisms from the environment, while sterilization refers to the elimination of all forms of microbial life.

Decontamination is the process to remove pathogenic microorganisms from objects for the purposes of safe handling and use. The CDC states that cleaning (i.e., removing visible material from surfaces) is a first step in the decontamination process so that organic or inorganic material does not interfere with decontamination. As outlined in this section, the use of sporicidal agents to manually clean healthcare environments is a form of both cleaning and decontamination. Use of touchless automated methods are solely for the purpose of environmental decontamination.

Recommendations applicable to environmental cleaning and decontamination include:

- Terminal room cleaning (cleaning after a patient is discharged or transferred from a room) with a sporicidal agent should be considered in conjunction with other measures to prevent CDI during endemic high rates or outbreaks, or if there is evidence of repeated cases of CDI in the same room.
- Daily cleaning with a sporicidal agent should be considered in conjunction with other measures to prevent CDI during outbreaks or in hyperendemic (sustained high rates) settings, or if there is evidence of repeated cases of CDI in the same room.
- Measures of cleaning effectiveness should be incorporated to ensure quality of environmental cleaning.
- Disposable patient equipment should be used when possible and reusable equipment should bethoroughly cleaned and disinfected, preferably with a sporicidal disinfectant that is equipment compatible.

The CDC guidelines for environmental cleaning and decontamination for C. difficile include the creation of daily and terminal cleaning protocols and checklists for patient-care areas and equipment. Other guidelines recommend frequent education for environmental service personnel in the primary language of the cleaning team and the use of various techniques to help improve cleaning and decontamination practice as outlined by the CDC (e.g., observation, fluorescent markers, and bioluminescence).

Safety practices for laundry, bedding, and other environmental services are included in the CDC's "Guidelines for Environmental Infection Control in Health Care Facilities." Guidelines for specific facility types, including hospitals, nursing homes, long-term acute care facilities, and outpatient facilities, are available from the CDC and other healthcare agencies.

Environmental cleaning as a safety practice

The healthcare environment is recognized as a primary source of *C. difficile* transmission. *C. difficile* is spread through the feces of infected and colonized patients. Patients with contaminated hands may spread *C. difficile* by touching surfaces in the healthcare environment. Some evidence suggests *C. difficile* may be dispersed to surfaces near the patient through droplets in the air. Transmission can occur when other patients, healthcare staff, or visitors touch contaminated surfaces and orally ingest *C. difficile* (e.g., while eating). Those who take antimicrobials, are advanced in age, or have compromised immune systems are at high risk of getting CDI from exposure to the pathogen. Others may become asymptomatic carriers of *C. difficile*.

Both symptomatic and asymptomatic carriers have the potential to contaminate the environment. In one hospital, *C. difficile* was recovered from 59% of samples in rooms of asymptomatic carriers and 75% of samples of rooms with patients with CDI.69 Patients may continue to contaminate the environment after treatment. The most contaminated areas, or "high-touch surfaces," include the bed rails, bed surface, supply cart, over-bed table, and intravenous pumps.

In one study, CHWs' hands were just as likely to be contaminated with *C. difficile* after touching high- touch surfaces as they were by touching a CDI patient. *C. difficile* produces spores that are especially robust and may remain viable in the environment for over 4 days.

Eliminating *C. difficile* in the healthcare environment requires specialized practices. Evidence shows that *C. difficile* spores are resistant to alcohol and many hospital disinfectants. In one study, exposure of the bacteria to low levels of certain cleaning agents resulted in higher CDI sporulation capacity (the ability for vegetative cells to forms spores during unfavorable environmental conditions).[70]

Among cleaning and decontamination agents for washing surfaces by hand, chlorine-releasing solutions (e.g., bleach), at sufficient concentration and with appropriate exposure time (at least 10 minutes), demonstrate the best evidence for killing *C. difficile*.[71]

Decontamination by hand is challenging and not always effective in reaching all contaminated surfaces in the healthcare environment. Automated touchless methods have been developed and implemented to supplement cleaning by hand and prevent the spread of CDI and other HAIs. The two most commonly studied touchless methods for *C. difficile* decontamination are hydrogen peroxide decontamination (HPD)—including vaporized, aerosolized, atomized, and dry mist systems—and ultraviolet disinfection (UVD), which includes UV radiation and pulsed xenon UV light systems. In laboratory studies, both methods have shown effectiveness in almost entirely eliminating *C. difficile* contamination from targeted surfaces.

Although subject to some debate, it is generally recommended that surfaces be precleaned by hand prior to use of UVD or HPD, as organic matter is thought to reduce the efficacy of the UVD and HPD methods. The UVD methods generally take less time than HPD to decontaminate a room.

There is increasing incentive for facilities to implement an effective environmental cleaning and decontamination program as facility rankings and CMS reimbursement rates are tied to reported rates of healthcare facility-acquired onset (HO CDI).

BEFORE MOVING ONTO THE NEXT SECTION, PLEASE COMPLETE CASE STUDY 4 ON THE NEXT PAGE.

Implementation: challenges and facilitators

One of the challenges reported across several of the studies on HPD and UVD was being able to use the touchless machines in all intended cases. For example, Levin et al. (2013) reported that the goal was to conduct terminal UVD on all contact precautions rooms but only 56% of discharged contact precautions rooms received the UVD treatment.[72] This discrepancy was due to limited device availability or the presence of a second room occupant.

Compliance with cleaning procedures is essential for eliminating active *C. difficile* from the environment. Research shows that touchless methods require appropriate operation. For example, the UVD machine may require repositioning in order to be most effective. Ways to assist with manual cleaning compliance include cleaning checklists and audit and monitoring.

Key findings

- The most-recommended cleaning and decontamination agents for manual use are chlorine-based solutions.
- The addition of hydrogen peroxide decontamination (HPD) or ultraviolet light decontamination (UVD) to standard cleaning is associated with significant reductions in facility-level CDI rates.
- HPD and UVD have drawbacks, including expense and the time it takes to decontaminate a room. However, the process for UVD is shorter than for HPD.
- The performance of environmental cleaning services staff is important and can be improved through the use of training, checklists, and audit and feedback.
- Future directions include research and development of nontoxic decontamination agents, new technologies, and research on patient outcomes and environmental cleaning in diverse healthcare settings.

Testing methods and *C. difficile* colonization

Patients with *C. difficile* shed *C. difficile* spores, which contaminate the environment and may infect other patients. Rapid identification of patients with CDI helps expedite contact precautions and isolation of these patients and prevent transmission to other patients. The symptoms of CDI often match those of other causes of diarrhea; therefore, early and rapid diagnosis is important to start the appropriate treatment and improve patient outcomes. Starting treatment and infection protocols sooner may ultimately reduce hospital length of stay, thereby reducing healthcare costs. Rapid diagnosis also ensures that providers modify any existing therapies, such as discontinuing antimicrobial agents, which could worsen a patient's condition.

Case Study 4: Xenon UV decontamination

Instructions: Spend 10 minutes reviewing the case below and considering the questions that follow.

Cooley Dickinson Hospital is a 140-bed acute care community hospital in western Massachusetts with mostly single-bed rooms. Like many hospitals, there was concern that contamination of patient rooms from previous occupants is associated with C. difficile infections. In 2011 the hospital began using two portable pulsed xenon ultraviolet (PPX-UV) devices in an attempt to reduce C. difficile incidence.[72]

Rooms and bathrooms were terminally cleaned as usual with a hospital-grade disinfectant product in most rooms and a chlorine-based product in C, difficile rooms. This was followed by the use of PPX-UV, for three 7-minute exposures (once in the bathroom and then in 2 locations in the main patient room). The overall room turn-over time was extended by approximately 15 minutes over a standard terminal cleaning because cleaning could continue in the main room during PPX-UV treatment of the bathroom. PPX-UV devices were also used in the operating suites (nights), emergency department (early mornings), and other clinical areas as available.

The PPX-UV device contains a xenon flash lamp that emits a broad spectrum of light covering the germicidal, or ultraviolet-C spectrum as well as the visible light spectrum. The device weighs approximately 150 pounds. The PPX-UV system produces a pulsed flash at a frequency of 1.5 Hz and a duration of less than 360 ms. The device is operated remotely in the hallway just outside the patient room and includes safety features such as motion sensors, which turn off the device if the door is opened.

Rates of C. difficile infections at Cooley Dickinson had been stable at an average of 9.22 per 10,000 patient-days for the years 2008 to 2010. In 2011, the year after the PPX-UV devices were used, the rate fell to 4.45 (53% reduction; P = 0.01). Of the 15 patients who were diagnosed with HA-CDI in 2011, 11 (73%) were placed in rooms that had not been treated with the PPX-UV device prior to occupation. Overall, 56% of discharged rooms received the UV light treatment. One reason some rooms were not treated was the simultaneous discharge of a number of patients and the limited number of devices. In addition, whereas most of the hospital's rooms are single occupancy, occasionally 2-bed rooms with 1 patient remaining could not be fully treated, although often the bathroom was treated. The authors concluded that the dramatic reduction in infection rates make the use of PPX-UV well worth investigating further in larger studies.

1. **Thinking about your own institution how effective do you think efforts are to prevent C. difficile infections? In what ways could those efforts be improved?**_____

2. **If you have had experience with PPX-UV devices, do you think these are a feasible technique for wider use? Why or why not?**

3. **What kinds of barriers to wider use of PPX-UV devices might need to be overcome?**_____

While testing accuracy and speed have improved in the last 10 years, there is currently no consensus onthe best testing method. It is helpful for clinicians to understand the strengths and limitations of the testing methods when interpreting test results. The testing methods have varying sensitivities and specificities, due to each test's detection ability and the tests' different detection targets.

Each class of test targets one of the following: *C. difficile* toxin, genes that produce toxin, or identification of toxigenic *C. difficile* in the stool. Detection of genes that produce toxins and toxigenic *C. difficile* indicates a patient may be colonized or infected with *C. difficile*. Detection of *C. difficile* toxin indicates infection. Each of the targets can indicate different stages in the progression of the disease. Some patients may remain colonized and acquire protection from disease while others progress to the disease. Some with symptoms may be treated and become asymptomatic carriers.

The criteria for whom to test for CDI such as the number and frequency of diarrheal stools that should trigger testing have decreased in the last few decades. Whole genome sequencing and molecular typing indicate that most CDI is acquired from sources other than symptomatic cases.

Asymptomatic colonized patients do not shed as many *C. difficile* spores as CDI patients; however, they still contaminate the environment. Evidence supports identifying asymptomatic colonized *C. difficile* patients for the purpose of isolation and contact precautions.

In the last decade, the most commonly used standalone test method has shifted from enzyme immunoassays to tests that detect DNA. Known as nucleic acid amplification testing, or NAAT, these tests generally have better detection abilities than enzyme immunoassays. A shift to more rapid and accurate testing results in less use of unnecessary CDI-targeted antimicrobials and a decrease in laboratory testing volume.

NAAT detects toxigenic *C. difficile* genes, not the damaging toxins, and may identify asymptomatic carriers as well as those with *C. difficile* disease; also, there is debate about whether the presence of toxigenic *C. difficile* alone is sufficient to diagnosis CDI. Guidelines therefore suggest that only symptomatic (i.e., those with diarrhea) patients should be tested.

To improve accuracy, combinations of tests are being used. Particularly if laboratories lack clinical input on specimen criteria and accept any unformed stool for testing, it may be most appropriate to use a combination of tests such as a test for organism combined with a relatively sensitive test for toxin in the stool. These combinations test for the toxigenic organism and test for the actual toxin.

Testing methods

CDI testing methods have different sensitivities and specificities, which impact CDI rates. A number of recent studies have shown that more sensitive molecular testing methods result in higher CDI surveillance rates. The improved sensitivity of molecular tests allows infected and colonized patients to be rapidly and reliably identified but can be "too good" at identifying patients who are colonized but not truly infected with *C. difficile*.

The following testing practices for suspected *C. difficile* in adults are recommended:

- Use patients with unexplained and new-onset ≥3 unformed stools in 24 hours as the preferred target population for testing for CDI

- Use a stool toxin test as part of a multistep algorithm (i.e., glutamate dehydrogenase [GDH] plus toxin; GDH plus toxin, arbitrated by NAATs; or NAAT plus toxin) rather than NAAT alone for all specimens received in the clinical laboratory when there are no pre-agreed institutional criteria for patient stool submission.
- Use NAAT alone or a multistep algorithm for testing (i.e., GDH plus toxin; GDH plus toxin, arbitratedby NAAT; or NAAT plus toxin) rather than a toxin test alone when there are pre-agreed institutional criteria for patient stool submission.
- Do not perform repeat testing (within 7 days) during the same episode of diarrhea and do not test stool from asymptomatic patients, except for epidemiological studies (strong recommendation, moderate quality of evidence).

Guidelines and systematic reviews recommend only testing symptomatic patients for *C. difficile,* except for the purpose of epidemiological studies. The recommendations are somewhat flexible with regard to the number of episodes of diarrhea that justify the need for CDI testing, noting that providers should take into account whether the patient has risk factors for CDI, most notable of which is antimicrobial use. Before testing, physicians should attempt to rule out other causes of diarrhea. Considerations with regard to repeat testing include the background prevalence of CDI at the facility. Guidelines also recommended that, while laboratory diagnosis is pending, treatment should be initiated empirically for patients who present with fulminant CDI or if obtaining the test results takes more than 48 hours. If test results cannot be obtained on the same day, patients with suspected CDI should be placed on preemptive contact precautions pending the *C. difficile* test results. As treatment recommendations differ, it is important to know the severity of the infection and whether it is an initial or recurrent episode.

An abdominal CT scan may be used to differentiate between CDI and other causes of colitis and to determine the extent of the disease. However, to diagnose regular CDI (e.g., while test results are pending), when an abdominal CT has poor sensitivity, endoscopy can be used in certain urgent situations. The American College of Gastroenterology guidelines recommend endoscopy when a rapid diagnosis is needed or an initial negative toxin assay when CDI is strongly suspected, when there is an ileus and stool is not available, or when other colonic diseases are in the differential diagnosis.[73]

Screening and isolation of asymptomatic carriers

Preemptively identifying hospital patients at risk for CDI, and for severe courses of CDI, has been proposed as a patient safety strategy. At the patient level, it is recommended to screen symptomatic patients primarily so that providers can identify those in need of CDI treatment.
The arguments in support of only screening symptomatic patients include:

- Screening asymptomatic patients requires significant laboratory resources,
- Studies on MRSA found that active surveillance was not more effective than enhanced infectioncontrol policies,
- Isolating asymptomatic CDI carriers requires additional hospital resources (e.g., single rooms), and
- Other interventions, such as hand hygiene, are effective at reducing multiple HAIs and are a better use of resources.

Several published studies, however, have found public health benefits from screening asymptomatic carriers. One quasi- experimental study and three simulations found that detecting and isolating asymptomatic carriers was associated with prevention of future cases. Screening and treating high-risk populations (regardless of CDI symptomology) is also explored in the literature. Some suggest that patients at high likelihood of being asymptomatic carriers not be tested but medical staff should use enhanced infection control practices such as the use of gloves. In addition, units or facilities with high likelihood of asymptomatic carriers should carry out CDI cleaning protocols.

Key findings about testing

- Some research supports universal *C. difficile* testing for hospitalized patients with diarrhea.
- Screening and isolating asymptomatic carriers can prevent CDI transmission but is resource intensive.
- NAATs of unformed stool have relatively accurate sensitivity and specificity.
- Concerns with NAATs include that they detect toxigenic *C. difficile* genes, not the actual damaging toxins and may capture colonized patients in addition to those infected with *C. difficile*.
- Certain multistep test algorithms (that include a test for *C. difficile* and for CDI toxins) perform as well as or better than NAATs but take longer.
- Tools that identify patient risk for CDI could be useful in preventing CDI.
- Tools that identify a high risk of severe CDI or mortality show promise for preventing severe CDI outcomes.

Multicomponent CDI prevention interventions

The most common component of multicomponent interventions is environmental cleaning and decontamination. Isolation of CDI patients and hand hygiene practices are the next most common components. Antimicrobial stewardship practices, contact precautions, testing and surveillance practices, and patient isolation/ cohorting are also common in multicomponent CDI prevention interventions. (Table 1)

Cross-Cutting Practices

Cross-cutting practices that can facilitate the success of a multicomponent intervention include the use of checklists and assigned roles, staff education, improved workflow systems, and communicating laboratory results and communicating CDI patient status through door signs.

In a study by Power et al. (2010), an 850-bed hospital implemented a multicomponent intervention that included antimicrobial stewardship, hand hygiene, environmental cleaning and decontamination, and education about CDI. In five wards with higher baseline CDI rates, there was an implementation of an "improvement collaborative," in which staff were broken into teams who planned, implemented, and measured the impact of selected PSPs as outlined by a systems improvement toolkit.[74]

Table 1. Multicomponent CDI Prevention Interventions

Intervention Component	Specific Practices
Environmental cleaning and decontamination	Increase in environmental services hours and training, dedicated CDI cleaning teams, cleaning equipment, dedicated equipment, disposable washbowls, dailyand terminal cleaning with bleach solution, terminal hydrogen peroxide decontamination, terminal curtain change, protocols and checklists
CDI patientisolation	CDI patient cohorts, private rooms for CDI patients, wards for CDI patients, rapidisolation
Hand hygiene	Removal of ABHRs, promotion of handwashing with soap and water when workingwith CDI patients, patient hand hygiene, hand hygiene observations/audits, installation of sinks
Antimicrobialstewardship	Discontinuation of nonessential antimicrobials, restriction of the use of clindamycin, cephalosporins, and quinolones, revised guidelines and formularies
Contact precautions	Use of gowns and gloves when working with CDI patients, limits on patientvisitors, empiric contact precautions
Testing	Testing at first sign of diarrhea, promotion of testing, new diagnostic assay
Surveillance	Tracking and classification of CDI cases, education, outbreak investigation

The five selected collaborative wards saw a 73% reduction in HA-CDI cases per 1,000 patient bed days after 3 months, and the rest of the hospital saw a 56% reduction in CDI cases per 1,000 patient bed days after 6 months.

Key findings about multicomponent interventions

- Multicomponent interventions to prevent CDI were associated with decreases in CDI rates.
- The most common component was environmental cleaning, followed by hand hygiene and patient isolation practices; antimicrobial stewardship and contact precautions; and CDI testing and surveillance.
- No single CDI prevention resource was used across studies.
- Information was limited on staff compliance andfinancial costs of interventions.
- Collaborations and teamwork were reported to be facilitators of implementation of multicomponent interventions.
- Additional facilitators of staff compliance included adequate supplies (e.g., gowns, soap), communication, signage, and institutional support. Barriers included time it takes to perform prevention practices (e.g., wash hands, put on gowns), inadequate staff education, inconsistency in testing criteria and unclear roles for ordering CDI tests, visitors notpracticing contact precautions, and lack of isolation rooms.
- Real-world studies on the implications of different practice combinations, as well as studies on regional prevention efforts and nonhospital settings, will help improve understanding.

Conclusions about interventions to prevent C. difficile infections

Antimicrobial Stewardship: ASPs are associated with decreases in CDI. Individual study outcomes were mixed, showing statistically significant decreases and statistically nonsignificant decreases/no change in facility- or ward-level CDI. Interventions included formulary restrictions, prescriber education, and audit and feedback/case review practices.

Significant reductions in CDI were associated with higher baseline CDI rates/outbreaks, ASPs developed specifically to reduce CDI (as opposed to ASPs focused on other clinical and microbiological outcomes), and ASPs that included restrictions to high-risk antimicrobials or a preauthorization component. Prescriber buy-in and staffing and technical resources were factors that impacted implementation.

Hand Hygiene: In laboratory testing, washing with soap and water outperforms ABHRs for removal of *C. difficile* spores from hands; ABHRs are not effective in killing *C. difficile* spores. It is the mechanical action of washing that removes the organism; therefore, proper handwashing technique is important. Hand hygiene is frequently framed as an HCW compliance issue, with studies measuring the impact of sink location and education on hand hygiene compliance. Patient hand hygiene initiatives show promise for helping prevent the spread of CDI.

Environmental cleaning and decontamination *for C. difficile* is associated with significant decreases in facility-level CDI rates in most studies. Practices with positive outcomes include daily and terminal cleaning of CDI patients' rooms with bleach solutions (typically 5,000 ppm), and terminal bleach cleaning plus the use of no-touch decontamination methods such as hydrogen peroxide or UVD. The UVD process takes less time than the hydrogen peroxide method. Both methods require the room or area be vacant, which is an implementation challenge. Studies suggest that standardized cleaning protocols and training and observation of environmental cleaning services staff help improve cleaning and decontamination for *C. difficile*.

For CDI **surveillance,** using standardized and accurate case definitions is an important practice. Research using new technologies for *C. difficile* genotyping and ribotyping has helped identify outbreaks. Despite the role CDI surveillance plays in understanding epidemiology and informing prevention practices, CDI surveillance implementation is not well studied.

Testing. Rapid and accurate identification of CDI is important in order to initiate treatment and discontinue antimicrobials (if appropriate) for CDI patients. If test results cannot be obtained on the same day, patients with suspected CDI should be placed on preemptive contact precautions pending test results.

The evidence indicates that NAATs and multistep test combinations show best results. CDI risk- prediction tools show promise for preemptive intervention. There are different perspectives on whether to test for (and subsequently isolate) asymptomatic carriers; However, some studies show this practice is resource intensive.

Multicomponent CDI prevention interventions included environmental cleaning, hand hygiene, patient isolation, antimicrobial stewardship, testing, and surveillance, as well as other PSPs and cross-cutting strategies. Studies consistently show associations between multicomponent interventions and statistically significant reductions in CDI. Factors that facilitated implementation of multicomponent interventions included the use of checklists and assigned roles, staff education, and collaboration and teamwork.

Minimizing exposure to invasive devices and reducing device-associated risks

An invasive device is any medical device that is introduced into the body, either through a break in the skin or an opening in the body. Invasive devices include catheters, such as urinary catheters or central venous catheters, and endotracheal tubes used for mechanical ventilation. Medical catheters are tubes that serve purposes such as administering fluids, blood products, medications, and nutritional solutions; providing hemodynamic monitoring; and collecting urine and measuring urinary output. Endotracheal tubes are inserted into a patient's trachea to provide an unobstructed passageway for oxygen and other gases (e.g., anesthesia) while a patient is mechanically ventilated.

The use of invasive devices in patients, while often medically necessary, has been associated with increased risk of invasive infections (e.g., bloodstream infections) and overall mortality. From 2011 to 2014, catheter-associated urinary tract infections (CAUTIs), central-line associated blood stream infections (CLABSIs), and ventilator-associated pneumonias (VAPs) accounted for 38%, 24%, and 2% of all healthcare-associated infections, respectively.[75] The treatment of these infections is often complicated by resistance to commonly used antibiotics. Within these three categories of infections (i.e., CAUTIs, CLABSIs, and VAPs), the percentage of pathogens that exhibited drug resistance varied depending on species and antibiotic, but an estimated 14% percent were caused by an antibiotic-resistant pathogen.

Catheters

To reduce the harms associated with catheter use (intravascular or urinary catheters), interventions can target several stages of their use:

- Avoiding unnecessary and inappropriate catheter use
- Ensuring aseptic placement of catheters
- Maintaining awareness and proper care of catheters in place
- Promptly removing unnecessary catheters

A systematic review by Patel et al. (2018) reviewed 102 studies with interventions aiming to reduce CAUTIs and CLABSIs.[76] The review determined that the most successful interventions targeted multiple stages. For both CAUTIs and CLABSIs, successful interventions included protocols to remove by default based on certain criteria (e.g., time).

Published guidelines have various recommendations for reducing harm throughout the phases of the patient's care, including:[77]

- Timing of catheter placement
- Selection of the appropriate catheter device
- Use of hand hygiene
- Aseptic technique strategies
- Barrier precautions during device placement and care
- Use of systemic antibiotics (not recommended) and antibiotic lock solutions

Urinary Catheters

Specific to urinary catheters, Mody et al (2017) conducted a large-scale before-and-after intervention study of 404 nursing homes that implemented a multicomponent strategy that included targeting multiple stages of device use.[78]

This study of community-based nursing homes used the Comprehensive Unit-based Safety Program (CUSP) toolkit for CAUTI, developed as part of the Agency for Healthcare Research and Quality Safety Program for Long-Term Care. The intervention targeted urinary catheter removal, aseptic insertion, incontinence care planning, and various training programs for staff, patients, and family.

The intervention reduced UTIs, perhaps indicating success in aseptic techniques, but did not reduce overall catheter utilization. The authors theorized that catheter utilization in nursing homes across the country was already relatively low at the start of the study, leaving little room for further reductions.

Intravascular Catheters

With respect to intravascular catheters, certain patient safety practices can be used to reduce the risk of infection when vascular access cannot be avoided. The practices focus on the use of antibiotics or specialized catheters that contain antimicrobial substances. The section below discusses these practices in further detail and their implications for antimicrobial resistance and other potential patient harm.

The CDC guidelines for preventing intravascular catheter-related infections provide recommendations for antibiotic and antiseptic use. In general, for intravascular catheters, the CDC does not recommend the use of systemic antimicrobial prophylaxis. Instead, the CDC recommends the use of certain antiseptic ointments at the catheter exit site for dialysis catheters and recommends antibiotic locking solutions in certain situations.

Regarding site placement of central venous catheters (CVCs), one systematic review of published ICU infection outbreaks found strong evidence to support the use of subclavian insertion sites compared with jugular or femoral sites to reduce the risk of CLABSI.[79] This practice is strongly supported by the CDC guidelines to avoid use of jugular or femoral insertion sites.

As with most medical procedures that are physically invasive, sanitary practices are necessary and may reduce the risk of infected wounds and invasive infections. While no study specifically addressed sanitary practices as an intervention, the CDC guidelines include detailed instructions on appropriate infection control procedures for intravascular catheters. The strongest CDC recommendations include:

- Using sterile gloves when inserting arterial, central, and midline vascular catheters
- Frequently performing hand hygiene
- Using sterile gauze or sterile, transparent, semipermeable dressing to cover the catheter site
- Using chlorhexidine antisepsis for insertion sites in specific cases (see guidelines for details)

One method of combating invasive infections associated with catheters is to reduce and restrict the growth of bacteria within the catheter itself. Bacteria often form biofilms within catheters that can inhibit catheter function and increase the risk of infection. In addition to preventing bacterial infections and biofilm formation, antibiotic lock (ABL) therapy reduces costs and vein damage associated with device replacement. ABL therapy is the insertion of a concentrated antibiotic solution into a catheter lumen (its internal channel or tube) to prevent the development of microbial biofilm on catheter surfaces.

In a study by Dixon et al. (2012), ABL therapy, as an adjunct to systemic antibiotic therapy, vs. systemic antibiotic therapy alone in patients with tunneled hemodialysis catheters, reduced CLABSI incidence by over 50% and reduced treatment failure and relapses in the study group compared with the control group.[80] The CDC recommends that ABL prophylaxis only be used for hemodialysis patients with long-term catheters who have a history of multiple CLABSIs despite appropriate aseptic techniques during catheter care and insertion.

Catheter Innovations To Reduce Risk of Infection

Various catheter materials have been studied to determine their effectiveness at reducing biofilm formation and preventing catheter-related infections. Urinary catheters can be made of hydrophilic materials—which reduce friction during insertion, thus reducing the need for lubrication and the risk of urethral damage—or impregnated with antimicrobial chemicals to prevent colonization of the catheter with bacteria or fungi. Catheters can be constructed of latex, silicone, or other components; however, antimicrobial silver alloys may bind more readily to latex than to other materials.

Three technologies have been found to be successful in laboratory experiments: gum arabic capped-silver nanoparticle-coated devices; catheters impregnated with rifampicin, triclosan, and trimethoprim; and CVCs impregnated with minocycline and rifampicin (M/R) + chlorohexidine (CHX). Gel reservoir and hydrophilic catheters may be safer than traditional sterile noncoated catheters.

Silver-impregnated catheters have mixed evidence of efficacy. Catheters impregnated with both silver and chlorohexidine have been demonstrated to reduce colonization and CLABSIs, especially in settings with high background rates of CLABSIs and are highly recommended by CDC if the CVC is expected to stay in place for more than 5 days.

Another innovation for increasing catheter safety is the use of needleless connectors. If needleless connectors are used, the CDC strongly recommends that an antiseptic be used to scrub the access port and that it be accessed only with sterile devices.

The CDC acknowledges the benefits of antibiotic-impregnated or antiseptic-impregnated urinary catheters in certain situations but also addresses a mix or lack of evidence demonstrating that they reduce UTI. The CDC also states that silicone and hydrophilic catheters may be preferable in certain situations (e.g., hydrophilic catheter use for intermittent catheterization).

Reducing Ventilator-Associated Infections

Supraglottic suction refers to suctioning that removes bacteria-laden secretions to reduce the risk of aspiration pneumonia or upper-respiratory tract pneumonia. A systematic literature review by Doyle et al. (2011) found that the current literature supported the PSP of supraglottic suction in a patient's endotracheal tube.[79] The authors also found overall support in the literature for bed elevation of 30 to 45 degrees for mechanically ventilated patients. They also found supporting evidence for selectively decontaminating patients' digestive tract to prevent VAPs. All three of these PSPs— supraglottic suction, bed elevation, and selective decontamination—aim to reduce aspiration of bacteria in respiratory fluid and thus reduce pneumonia in ventilated patients.

Subglottic secretion suctioning is a similar method to reduce ventilator-associated infections and was found by one randomized control study to be associated with lower rates of VAP and overall lower length of required ventilation.

The same systematic literature review found only mixed evidence to support using topical antibiotics to decontaminate the oropharynx of patients on mechanical ventilation.

The Society for Healthcare Epidemiology of America (SHEA) and Infectious Diseases Society of America (IDSA) guidelines, "Strategies to Prevent Ventilator-Associated Pneumonia in Acute Care Hospitals," state that there is moderate evidence to support the use of endotracheal tubes with a subglottic suction catheter for patients ventilated for more than 2 to 3 days but do not recommend closed/inline endotracheal suctioning.[81] These guidelines also note that the quality of evidence was low to support the bed elevation discussed by Doyle et al. and that the quality of evidence was high for selective oral or digestive decontamination.

The guidelines suggest the following additional PSPs for adult patients:

- Assessing the readiness to extubate daily
- Interrupting sedation daily
- Performing spontaneous breathing trials with sedatives turned off
- Changing the ventilation circuit only if visibly soiled or malfunctioning

PSPs with moderate quality of evidence include managing patients without sedation whenever possible, facilitating early mobility, administering regular oral care with chlorhexidine, and providing prophylactic probiotics.

Evaluation and Monitoring of Device Use

To reduce duration of device use, clinicians often must regularly reevaluate the need for the device andmonitor any changes (e.g., the patient's dependence on the device).

In the previously referenced systematic review, Patel et al. (2018) found that successful interventions aiming to reduce CLABSIs and CAUTIs often used checklists, auditing, and monitoring and focused on removal of devices. These checklists and monitoring procedures help reduce human error during the maintenance and removal of devices.

The CDC guidelines for intravascular catheters also provide recommendations on device removal and care. These include assessment of an insertion site infection, removal of unnecessary catheters, quick replacement of catheters when aseptic technique cannot be ensured, and appropriate length of time to use certain types of catheters (e.g., up to 14 days for umbilical venous catheters).

The CDC also has various recommendations on the evaluation and monitoring of device use for urinary catheters. These guidelines include the removing urinary catheters for operative patients as quickly as possible (<24 hours if possible), reducing kinking and obstruction of catheter tubes, and implementing guidelines to advise on proper catheter maintenance.

Lastly, the SHEA/IDSA guidelines include several recommendations on evaluation and monitoring of ventilator use. Some of these recommendations include changing the ventilator circuit if it is visibly soiled or malfunctioning, minimizing breaks in the ventilator circuit, and assessing the readiness to extubate daily.

Unintended Outcomes

Some of the above interventions, such as ABL solutions, topical skin ointments, and oropharynx decontamination involve the use of antibiotics. As with any antimicrobial use, overuse and inappropriate use can lead to increased drug resistance and increased risk of MDRO colonization or infection.

Regarding ventilator-associated antibiotic use, one before-and-after study discussed the effectiveness of selective digestive decontamination using polymyxin, tobramycin, and amphotericin B in the oropharynx and the gastric tube plus a mupirocin and chlorhexidine regimen in intubated patients. This study maintained that use of antibiotics in this scenario did not confer antibiotic resistance, but evidence showed that this practice increased the risk of MRSA infection and tobramycin resistance in aerobic Gram-negative bacilli such as P. aeruginosa and Enterobacteriaceae.[82] The SHEA/IDSA guidelines recommend that facilities with high levels of antimicrobial resistance not use digestive decontamination until higher quality, long-term studies are performed to assess the risks.[81]

For intravascular catheters, the CDC states that antibiotic ointments and creams should not be used on insertion sites (other than dialysis catheters) because of the risk of conferring antimicrobial resistance and fungal infections. Chlorhexidine dressings are appropriate in some cases.

When considering the use of antibiotics to prevent CLABSIs, CAUTIs, or VAPs, clinicians should exercise caution and be diligent about referencing the existing guidelines, which specifically warn against or promote antibiotics for certain uses and populations. Further research is needed on long-term effects of antibiotic use for selective digestive decontamination and long-term use of locking solutions.

Education To Reduce Device-Related Infection Risk

Ongoing education of patients, staff, and caregivers can also help reduce the harms associated with device use. The CDC recommends several education and implementation interventions for staff and patients to help improve outcomes associated with device use. Further, the CDC advises allowing only individuals (including family and at-home caregivers) trained in appropriate techniques for catheter insertion and maintenance to perform these tasks. Other agency recommendations include quality improvement programs to provide ongoing training for staff on all the PSPs discussed above: automated alerts to reassess the need for device use, written guidelines, auditing and feedback of staff practices, and periodic training on insertion, maintenance, and removal.

The SHEA/IDSA guidelines also state that staff education can help maintain high levels of compliance with recommended practices. Staff educational activities include workshops, hands-on training, and use of multiple modalities to convey information. Making information accessible in pocket pamphlets, posters, flowsheets, and other readily available modalities is also suggested. Finally, these guidelines state that educating patients and family on ventilator-associated guidelines can help them engage with and support the medical team's care.

Key findings related to invasive devices

- Using devices minimally and appropriately and practicing hygiene and infection control precautions when inserting them are basic steps that can be taken to reduce device-associated infections.
- Further research is needed to determine the safest and most effective uses of antimicrobial lockingsolutions and catheter materials.
- Antimicrobial resistance has not been eliminated as a concern when using antibiotics in antibiotic locking solutions, impregnated catheters, or prophylactic treatment to prevent infections.
- Ongoing implementation education, monitoring, and feedback for medical staff, patients, and caregivers are recommended for improving adherence to recommended PSPs.

Infusion Pumps

Use of infusion pumps, and increasingly smart pumps, has become standard practice in hospitals to administer critical fluids to patients. However, there is still limited research on best practices for reducing errors and improving infusion pump use through workflow and process changes as well as education and training. Infusion pumps are used to administer fluids such as nutrients or medications to patients.

In comparison to manual administration of fluids, infusion pumps provide the advantage of controlled administration—the ability to deliver fluids in small volumes or at precisely programmed rates or intervals.

Many newer infusion pumps are equipped with predetermined clinical guidelines, dose error reduction systems (DERSs), and drug libraries that provide a comprehensive list of medicines and fluids with dose, volume, and flow rate details. These "smart pumps" are designed to address the programming errors that traditional pumps are susceptible to by notifying a user when there is a risk of an adverse drug interaction or when the pump's parameters are set outside of specified safety limits for the medication being administered. Alerts generated by smart pumps include clinical advisories, soft stops, and hard stops.

Clinical advisories provide information about medications within the administering facility's drug library, including prompts for correct administration, which are programmed into the pump by the facility or larger organization. Soft stops notify users that a selected dose is outside of the anticipated range for a specific medication. These alerts can be overridden without changing the pump's settings. Hard stops alert users that a dose is out of the institution's determined range and prohibit the infusion from being administered unless the pump is reprogrammed.

As infusion pump technology continues to evolve, use of smart pumps in hospitals has increased. Along with this increase, many national organizations have identified implementing smart pumps as a key patient safety tool. The Institute for Safe Medication Practices (ISMP) strongly supports the use of smart pump safety features, and in 2006, the Institute of Medicine identified adoption of smart pumps as a strategy hospitals can use to help reduce the frequency and severity of medication errors.[83] Despite the growing support for the use of smart pumps as a safety strategy, however, the literature shows varying results for the effect they have on reducing medication errors. User error, inadequate use of safety technology, incorrect programming, and equipment failures can still occur, significantly impacting patient safety.

Potential harms

The infusion pump, along with its failures and user errors, can have significant implications for patient safety because of its ubiquitous nature and frequent use to administer critical fluids. Infusion-associated medication errors are mistakes related to ordering, transcribing, dispensing, administering, or monitoring drugs.[84] From 2005 to 2009, the U.S. Food and Drug Administration (FDA) received approximately 56,000 reports of adverse events related to the use of infusion pumps, and manufacturers conducted 87 infusion pump recalls. Fourteen of these recalls were categorized as Class I, in which there is a reasonable probability that use of the recalled device will cause serious adverse health consequences or death.

Although many of the events reported to the FDA were related to deficiencies in device design and engineering, user errors also occurred. One study found that almost half of all infusion-associated medication errors were attributed to deviations in following procedures and documentation requirements.[84]

Intravenous (IV) infusions in particular pose risks to patient safety due to their complexity and the multiple steps required in their administration. Studies have found that IV infusion is associated with 54% of all adverse drug events, 56% of medication errors, and 61% of serious and life-threatening errors.[85] In addition, IV medications are twice as likely to be involved in errors that cause harms when compared to medications delivered via other routes.

Smart infusion pumps have been implemented to avert possible medication errors; however, the risk of programming errors and equipment failures has not been eliminated. For example, one study found that despite use of smart pumps, 67% of the infusions evaluated involved one or more discrepancies.

Studies have shown that infusion pumps can contribute to inefficiencies and lead to errors. This is largely due to time-consuming, indirect patient care tasks associated with infusion pumps, such as searching for available pumps, priming tubing, manual pump programming, responding to false or unnecessary pump alarms, and managing tangled tubing. Inadequate workflows for these tasks can impede communication and cause unnecessary rework, delays, or gaps in care, all which impact patient safety. Organizations must also consider how new technology, such as smart pumps, affects workflow and is best implemented in order to drive toward safer use processes. Successful implementation often requires organizational commitment, a shared vision, an understanding of the risks and strengths of current processes, and a unified design that includes all systems and stakeholders.

Implementation

Changing processes or redesigning workflows for infusion pumps can be a complex undertaking that includes a variety of interventions. Standardization and streamlining of processes and workflows were identified as main facilitators of optimal infusion pump use across multiple studies. For example, one study found that a hospital was able to significantly improve utilization of IV infusion pumps by streamlining its workflow for cleaning and restocking pumps.

The implementation of smart pumps should be viewed as part of a larger safety initiative rather than just a technology upgrade and to be successful, implementation should focus on design of workflows. For example, implementing design-oriented solutions that constrain users to follow the preferred workflow, such as defaulting users into using the drug library, helps ensure users employ the safety features.

In addition, engaging multiple members of the care team in workflow redesign is an important facilitator. Clinical pharmacists play a key role in reducing error rates and should be consulted when configuring workflows. In some cases procedural deviations are not representative of inadequate care practices but rather demonstrate a poor fit between hospital policy and everyday practice. If workflows do not align with new technology or policies are implemented that are not compatible with natural workflows, then errors or workarounds can occur that impact patient safety.

Staff buy-in and hospital resources can pose barriers to process changes. When implementing infusion pump technology, organizations need to ensure that adequate infrastructure and resources are available, and that the affected staff believe that the change is worth the time and money required. More implementation studies are needed to understand best practices for reducing errors and improving infusion pump use through workflow and process changes.

Staff education and training

The literature shows that inadequate training is often associated with knowledge and rule-based mistakes when using infusion pumps. These medication errors can occur when staff are inexperienced, including being unfamiliar with the medication, environment, procedure, or equipment. In addition, lack of training can lead to overriding of smart pump safety features erroneously. Although smart pumps can be a beneficial tool to reduce medication errors attributed to manual programming, using the embedded drug libraries and DERSs is not mandatory.

The literature shows that nurses commonly bypass the safety features because the drug library parameters are not customized for their patient population, it takes too much time to program the pumps, and there are too many alarms. To prevent overriding safety features and programming errors, some hospitals invest in initial and ongoing staff training on the correct use, maintenance, and monitoring of smart pumps. Hospitals may also implement standard procedures for pump management and provide education on the use of the standardized protocols.

The FDA recommends providing training and educational activities for all employees designed to promote the safe use of infusion pumps, including drug library usage, as a risk-reduction strategy for facility administrators and managers. In addition, organizations should establish a standard approach for staff training and ensure that the education provided emphasizes the intended safety benefits.

Facilitators and barriers

The type and content of education provided are important facilitators to successful implementation. For example, education from the device manufacturer alone may be insufficient and implementing a hands-on training targeting identified obstacles can be essential to increasing use of safety features. In order to be most successful, the training program should include opportunities for participants to apply learning through discussing case examples. Training should also provide information about the most relevant smart pump functions and the potential challenges nurses may encounter in using them. Virtual training systems have been shown to facilitate learning, although the results are mixed.

In addition to the type of training, the choice of trainer can be a facilitator. Implementing a nurse champion-led group may improve smart pump compliance, and training that focuses on "why" smart pumps are used instead of just "how" to use smart pumps is important to increase adherence. By understanding the safety software, nurses are able to provide ongoing evaluation on needed revisions and refinements.

Limited knowledge transfer and constrained hospital and staff resources are potential barriers to implementation. For example, when nurses move to different wards, they are often exposed to new devices on which they have not been trained. In addition, after nurses are trained, they may not retain competency on use of a particular type of smart pump if they commonly use multiple types of pumps or if they infrequently use any pumps. Furthermore, establishing hospital-wide education programs can be a significant undertaking for staff development departments, and the time and energy constraints on nurse educators should be carefully considered and planned.

Resistance to culture change is also a potential barrier. Despite being educated on the use of standardized pump programming, nurses may be resistant to a culture change from the old processes to a new two-person verification process. Implementing a nurse-led program focusing on promoting compliance, partnering with pharmacists, and supporting manual audits can help create a culture of safety.

Conclusions

Evidence shows that protocols and workflows are integral to proper technology use and therefore should be carefully considered when implementing new infusion pump technology. Studies support streamlining and standardizing workflows. However, more implementation studies are needed to better understand the impact of workflow changes and best practices for effective integration of processes and infusion pump use. The evidence also shows support for providing education and training on infusion pumps to promote safe use. In these studies, the type and content of education provided were highlighted as facilitators, while limited knowledge transfer and resistance to culture changes were identified as barriers.

Carbapenem-resistant Enterobacteriaceae (CRE)

CRE encompass a family of gram-negative bacteria that cause infections with high mortality rates and few therapeutic options due to their ability to confer resistance to many different antibiotics.

Different mechanisms cause the carbapenem resistance, with carbapenemase-producing CRE (CP-CRE) considered primarily responsible for the increase in the spread of CRE. CP-CRE produce enzymes that break down many antibiotics: penicillins, cephalosporins, monobactams, and carbapenems. This trait is most commonly seen in *Enterobacteriaceae*, which include clinically important bacterial species such as *Escherichia coli (E. coli*) and *Klebsiella pneumoniae*.

Because of the public health risk CRE poses, predominantly attributed to the rapidly spreading CP-CRE, healthcare facilities must implement stringent infection control practices to reduce CRE-associated transmission and to ensure that healthcare settings remain safe for patients. Many toolkits and guidance documents exist to assist healthcare workers and infection control specialists to design and implement their CRE prevention policies.

CRE is commonly associated with clusters and outbreaks in healthcare settings and is responsible for increasing morbidity, mortality, and healthcare costs worldwide. In the United States, 42 States over the past decade have had at least one type of CRE infection diagnosed in their medical facilities.

Carbapenem resistance can be transferred between patients and between different species of bacteria via plasmids, allowing the rapid spread of the resistance gene within healthcare and community settings. Although CRE are largely associated with nosocomial transmission, species within the *Enterobacteriaceae* family (such as E. coli) have been associated with community-acquired infections and outbreaks in the past. Therefore, as CRE becomes more prevalent, both nosocomial and community transmission should be considered when developing prevention efforts.

Mortality among patients with CRE infections can be as high as 40 to 50% due to both the severity of the infections and the lack of effective antibiotics with which to treat them. Because of their increasing global incidence and associated morbidity and mortality, the World Health Organization has identified CRE as critical pathogens requiring focused prevention research.[86]

Contact precautions to prevent CRE infections

Contact precautions are one of three types of transmission-based precautions to control the spread of infectious diseases, the other two being airborne and droplet precautions. Contact precautions are currently recommended to prevent nosocomial transmission of CRE for patients with known or suspected infections or at an increased risk of infection with CRE. Maintaining appropriate contact precautions can be challenging for patients undergoing procedures or those who are critically ill and require intensive patient care. Contaminated stool and bodily fluids can transmit CRE, making environmental contamination a concern for patients who are incontinent, who have draining wounds or secretions, or who require high levels of care. Patient transport within and between healthcare facilities also complicates strict adherence to contact precautions. However, when successfully implemented, contact precautions have been shown to reduce transmission of CRE in healthcare facilities.

Contact precautions include appropriate patient placement (e.g., single-patient spaces), use of personal protective equipment, a reduction in the movement and transportation of the patient, the use of disposable or dedicated patient-care equipment, and the frequent and thorough cleaning of patient spaces (especially high-touch surfaces and equipment in close proximity to the patient). Variations on implementation of contact precautions differ by setting, risk of transmission, and the type of care being provided.

- Some level of patient isolation should also be a part of contact precautions when feasible. This may include:
- Isolating carriers or individuals infected with CRE in single rooms with attached bathrooms
- Isolating carriers into rooms shared only by other patients colonized or infected with the same pathogen
- Cohorting staff (to reduce staff-to-patient transmission), defined as using a dedicated team of healthcare staff to care for patients infected with a particular multi-drug resistant organism (MDRO)
- Prioritizing patients at higher risk of transmission for single rooms, and rooming the remaining carriers or infected individuals together

Of these options, single patient rooms are always preferred whenever possible. The placement of appropriate signs outside patient rooms is essential to alert staff and visitors to the isolation status of the patient(s) whose room(s) they are entering.

In addition to the contact precaution practices described above—particularly during invasive procedures—contact precautions may include full-head protection and/or face masks. When feasible, individual supplies and equipment dedicated to a colonized patient should be used. However, more studies are needed to determine which variations or additions to contact precautions improve control of CRE transmission.

Initiating contact precautions

Contact precautions are often initiated following a positive screening test. Active screening using perirectal swabs or swabs of other body sites may be used to screen patients for CRE colonization for the purpose of initiating contact precautions. The European Centers for Disease Control and Prevention (ECDC) recommends active screening on admission to specific wards or units (e.g., oncology units), during outbreak scenarios, and upon admission to a hospital.[87]

Active surveillance (upon admission) may not be appropriate in all settings. In units that regularly perform contact precautions, such as ICUs, active screening may be unnecessary. For some organisms, such as extended-spectrum beta-lactamase (ESBL)-producing bacteria, active surveillance has not been found to reduce transmission. Active surveillance also may not be appropriate in settings where the prevalence is low. Passive surveillance may be sufficient to reduce transmission in low-endemicity settings—initiating contact precautions only if a CRE infection is identified during the course of clinical care, as opposed to screening upon admission.

Pre-emptive isolation relies on identifying CRE carrier risk factors at admission to the facility, which requires information about potential risks. The CDC recommends isolating patients who transfer from high-risk settings (e.g., hospitals in endemic areas or facilities with known outbreaks).

Further research is needed to design a decision tree or risk score that can be used as a simple and accurate screening tool in a variety of settings. A study performed at the Johns Hopkins Hospital found that despite their assessed risk factors at admission (history of vancomycin-resistant *Enterococcus,* methicillin-resistant *Staphylococcus aureus*, and/or multi-drug-resistant gram-negative organisms), 57 percent of CRE-colonized patients and 50% of patients colonized with CP-CRE were not isolated with contact precautions.[88] The Johns Hopkins study demonstrates that even with a review of a patient's history at the time of hospital admission, many CRE carriers are missed, and are placed on contact precautions only after a positive clinical culture is isolated. This type of study is valuable for determining the positive predictive value of existing methods for preemptively assessing risk, and similar research is needed to assess the risk prediction models suggested in other studies and guidance documents.

There is currently no global consensus on whether it is appropriate, or when it is appropriate, to discontinue contact precautions. The CDC recommends that contact precautions be continued indefinitely. However, some recommend discontinuation on a case-by-case basis if: (1) at least 6 months have elapsed since a positive culture, and (2) at least two consecutive negative cultures were collected at least one week apart.

BEFORE MOVING ONTO THE NEXT SECTION, PLEASE COMPLETE CASE STUDY 5 ON THE NEXT PAGE.

Implementation

Fostering a workplace environment that encourages consistent use of contact precautions requires multi-institutional stakeholder involvement. Local health departments and large health systems may mandate contact precautions for patients with CRE infections. On a facility level, administrators and infection control specialists should encourage appropriate contact precautions by implementing monitoring and compliance audits as well as education of staff, patients, and visitors.

Cross-sectional surveys have found that CRE acquisition is negatively correlated with workplace factors such as lack of staff engagement in infection control efforts and the impression that the work environment is overwhelming, stressful, and chaotic.

Case Study 5: Containing an outbreak

Instructions: Spend 10 minutes reviewing the case below and considering the questions that follow.

In March 2007, the Ministry of Health of Israel set up a committee of infectious disease experts to contain a national outbreak of carbapenem-resistant Klebsiella pneumoniae (CRKP) around the country. In May 2007 a multifaceted strategy was devised to prevent dissemination of CRKP at Soroka University Medical Center, a 1000-bed acute care tertiary hospital.[89]

The key elements of the strategy were an emergency department flagging system to identify high-risk patients, the building of a 12-bed cohort ward, the use of intensive active surveillances in high-risk wards, enforcement of compliance with hand hygiene, contact precautions, and disinfection protocols, and a carbapenem-restriction policy.

The intervention produced an "enormous impact on patient location, surveillance cultures, and antibiotic policies and a massive investment in infection control resources." A total of 10,680 rectal cultures were performed for 8,376 patients, which identified 433 (5.16%) patients who were CRKP-colonized and 370 (4.4%) who were CRKP-infected. 789 (98%) of 803 patients were admitted to the CRKP cohort ward.

The CRKP infection density was reduced from 5.26 to 0.18 per 10,000 patient-days and no nosocomial CRKP infections were diagnosed. Carbapenem (meropenem) use was reduced from 283 to 118 defined daily doses per 1,000 patient-days.

1. **Do you think such an aggressive multifaceted intervention strategy was necessary to contain this outbreak? Why or why not?**

2. **Which of the measures undertaken as part of this effort do you think was the most important? The least important?**

3. **If you have been a clinician involved in trying to contain an outbreak of an antibiotic-resistant strain of bacteria, what lessons did you learn? Do you think the lessons are applicable to other healthcare settings?**

Efforts should be made to engage staff in infection prevention and to ensure that understaffing and disorganization are not hindering these efforts.

Training, monitoring, compliance auditing, and feedback systems are also effective for improving compliance and appropriate use of contact precautions. The CDC recommends that healthcare facilities implement policies for important CRE prevention practices such as hand hygiene and antibiotic stewardship, and that policies be enforced through continuous monitoring, auditing, and feedback. Additionally, the CDC recommends that facilities strictly enforce CDC guidance for CRE detection, prevention, tracking, and reporting.

Education must accompany any new policy to ensure effective implementation. Awareness about infection control policies is crucial to consistently and successfully implementing these procedures. Staff education has been part of several intervention efforts that have been successful in reducing CRE transmission.

Conclusions

Contact precautions are strongly recommended for patients infected with or colonized by CRE. There is little evidence to support universal active surveillance for CRE. However, active surveillance is recommended in outbreak scenarios, in highly endemic regions, and in healthcare facilities or units with ongoing transmission. In units already using universal contact precautions, the evidence suggests that active surveillance does not have a significant impact on reducing transmission. There is little evidence to support preemptive contact precautions for high-risk patients, however, it is recommended that CDC guidelines be followed for this practice.

In all settings, ongoing monitoring, staff feedback, and education on the implementation of contact precaution and infection control policies are highly recommended. They are often part of successful multi- faceted interventions.

There is no strong support for discontinuation of contact precautions when an individual has been placed on contact precautions due to a positive CRE culture. Such patients should remain on contact precautions at each healthcare facility they are admitted to until they are discharged into the community.

Harms due to anticoagulants

Anticoagulants are a critical therapy in the prevention and treatment of various types of thromboembolic disorders. Key indications for anticoagulants include the prevention of stroke among patients with chronic atrial fibrillation, and prevention and treatment of venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism. Anticoagulants include vitamin K antagonists (e.g., warfarin); heparin (unfractionated and low-molecular weight heparin); and novel oral anticoagulants (NOACs), such as direct thrombin inhibitors (e.g., argatroban and dabigatran) and factor Xa inhibitors (e.g., apixaban, rivaroxaban).

Anticoagulants have been consistently identified as the most common cause of adverse drug events (ADEs) in health care settings. Bleeding is the primary ADE of concern for anticoagulants, but they require a careful balance between thrombotic and hemorrhagic risks.

Anticoagulation management services

An anticoagulation management service is a systematic and coordinated approach to anticoagulation care delivery by a single provider following a physician- approved protocol. For example, these may be pharmacist- or nurse-led "anticoagulant clinics," in which patients are seen in an ambulatory setting on a regular basis to closely monitor bleeding and clotting laboratory values and adjust medications accordingly.

A range of models for anticoagulation management services exist. Most are pharmacist led, but some are led by nurse practitioners, physician assistants, nurses, or pharmacy technicians.

Overall quality of evidence for the efficacy of anticoagulation management services is moderate to high, given the number of randomized controlled trials and non- randomized controlled trials with comparison groups or pre/post designs. There have been several recent systematic reviews of pharmacist-led anticoagulation management services compared with usual care or other models. Evidence shows that the effect of anticoagulant management services on time to therapeutic range is moderately positive, but evidence is low or mixed onbleeding events and thromboembolic events.

Use of dosing protocols or nomograms for newer oral anticoagulants

The introduction of NOACs, including the direct thrombin inhibitors (DTIs) (e.g., dabigatran, argatroban) and factor Xa inhibitors (e.g., rivaroxaban, apixaban), may be associated with lower rates of some bleeding events compared with warfarin; however, the direct thrombin inhibitors are associated with a higher risk of major bleeding when used for management of heparin-induced thrombocytopenia. While NOACs may offer different risks and benefits from older oral anticoagulants, careful dosing to balance the risks of thrombotic and hemorrhagic adverse events is required for NOACs, just as it is for older drugs.

A protocol or nomogram is a dosing tool that specifies the proper amount of drug (e.g., dose, infusion rate) to be given to a patient based on specific criteria (e.g., patient characteristics such as weight, kidney or liver function, laboratory results). The goal of a dosing protocol or nomogram is to rapidly achieve and maintain a therapeutic range while guiding dosage adjustments and minimizing subtherapeutic or supratherapeutic concentrations. The use of dosing nomograms has been shown to improve the safety and effectiveness of older anticoagulants, particularly heparin therapy. Dosing protocols or nomograms are used for many drugs with a narrow window between their effective doses and doses at which they produce adverse effects; examples include several antibiotics (e.g., gentamicin, vancomycin) as well as anticoagulants (e.g., warfarin, heparin). Dosing protocols or nomograms may reflect different patient characteristics, such as kidney or liver function, depending on how a drug is metabolized.

Interventions to support safe transitions and continuation of patients' anticoagulants post discharge

Transitioning patients from one setting to another is a particularly vulnerable time when safety lapses can result in negative clinical outcomes, preventable adverse events, and avoidable hospital readmissions. The Joint Commission describes transitions of care as "the movement of patients between healthcare practitioners, settings, and home, as their conditions and care needs change."90 Care transitions can also be cause for concern with anticoagulants, given they are the most common causes of ADEs in healthcare settings. Anticoagulants vary in their complexity, dosing, and requirements for transitioning to home from a hospital or ED.

Conclusions about harms due to anticoagulants

There appears to be moderate evidence of pharmacist-provided anticoagulation management services, as well as some, albeit limited, evidence of different models being as effective. The studies of dosing protocols for the NOACs are largely observational, non-RCT studies without control groups or tests of significance, and with very small sample sizes. Thus, there is insufficient evidence to indicate the effectiveness of using dosing protocols/ nomograms for NOACs to prevent bleeding. There is a paucity of literature and strong evidence on interventions, services, and programs for the safe transition of anticoagulant therapy post discharge from the hospital or ED.

Harms due to diabetic agents

Individuals who have diabetes are not usually hospitalized for glucose control but are for other acute and chronic conditions. As inpatients, they are at risk for hypoglycemia and hyperglycemia by having their blood glucose levels (BGL) outside the recommended ranges for hospitalized patients (a target glucose range of 140–180 mg/dL); they may not have available or be consulting with a specialized diabetes or glucose management team skilled in diabetes medication administration. Diabetes exacerbations are known to contribute to morbidity and mortality, and can be avoided through better medication management, including through the use of standardized insulin protocols. During the past decade, the United Kingdom—more than any other n ation—has documented diabetes medication errors through the National Diabetes Audit and instituted quality improvement projects to reduce errors and improve outcomes.[91] The data compiled through the National Diabetes Audit constitute one of the best sources of information on safety practices and are referred to below.

Diabetes is a growing chronic condition in the United States. Ambulatory patients with diabetes too frequently experience poor management of BGL, hypoglycemia (blood glucose below 70 mg/ dL) and hyperglycemia (200 mg/dL or a fasting blood glucose level above 126 mg/dL).

The clinical standards regarding BGL have evolved over the past two decades, beginning with a 2001 landmark study by Van den Berghe that documented increased morbidity and mortality due to hyperglycemia in the inpatient setting.[92] The study catalyzed a change in inpatient diabetes medication management toward standard protocols based on the American Diabetes Association's recommendations and away from the practice of sliding-scale insulin. In addition, there has been a move away from aggressive glycemic targets; adherence to strict targets has led to an increase in episodes of hypoglycemia. Tight glucose control is not indicated in the hospital setting. BGL <180 mg/dL is associated with lower rates of mortality and stroke compared with a target glucose <200 mg/dL, whereas no significant additional benefit was found with more strict glycemic control (<140 mg/dL). Thus, the ranges for acceptable BGL have eased over time.

There are numerous reasons that standardized insulin protocols or other ways of reducing medication administration errors are important patient safety practices (PSPs). A growing number of aging U.S. adults have diabetes, contributing to increases in the number of inpatients with multiple chronic conditions, which make diabetes even more difficult to manage and control. If diabetes is well controlled during inpatient stays, other conditions can be more effectively treated and instances of BGL out of recommended range can be reduced. These practice changes have implications for inpatient costs, quality of care, readmission rates, and patient reported outcomes.

Standardized insulin protocols

Standardized protocols are used in many situations because they reduce variability in human behavior and thus reduce the chance of error. Standardized insulin protocols and the insulin regimens to which they apply are intended to maintain relatively constant BGL in a person and reduce fluctuations. However, insulin medication must be adjusted based on an individual's activity and nutrition intake; an insulin bolus may be needed at mealtime, for example. Insulin regimens include basal insulin or a basal plus bolus correction insulin, which is the preferred treatment for non-critically ill hospitalized patients with poor oral intake. An insulin regimen with basal, prandial, and correction components is the preferred treatment for non-critically ill hospitalized patients who are able to intake nutrition orally.

Standardized protocols are implemented through different forms, including specialized medical teams and paper and electronic order sets. Sole use of sliding-scale insulin in the inpatient hospital setting is strongly discouraged.

Teach-back in diabetes medication management

The teach-back method is also called "closing the loop" and can be effective in increasing patients' ability to retain knowledge that helps them manage health conditions. Teach-back tests comprehension by asking patients to say in their own words what they understand the clinician has instructed them to do. Teach-back has been used with many different kinds of patients and in multiple settings, but to be effective, the patient must have the cognitive ability to comprehend the information, the physical skills to successfully self-administer insulin and other diabetes medication, be able to perform self-monitoring of blood glucose, and have adequate oral intake. The setting for teach- back is typically outpatient.

Conclusions about diabetic agents

Diabetes is a growing chronic condition in all age groups, and strategies for improving medication management will have significant impact on mortality and morbidity. Using standardized insulin protocols to reduce hypoglycemia in the hospital and teach-back methods in other settings to improve the ability of diabetes patients to better understand and self-manage their own insulin and other antihyperglycemic medication needs are both patient safety practices that have potential.

There is more and stronger evidence to support standardized hospital insulin protocols to prevent hypoglycemia than there is to support teach-back methods to improve medication management. Teach-back is in a formative stage in that enhanced definitions and typologies of teach-back methods are needed before it will be possible to collate the clinical evidence. However, better-designed studies on both patient safety practices are needed to establish a firm evidence base.

Reducing adverse drug events in older adults

People are living longer than ever. In the United States, the number of Americans age 65 years and older increased from 37.2 million in 2006 to 49.2 million in 2016 (33% increase) and is projected to reach 98 million by 2060. With age comes the likelihood of increasing morbidity. An estimated 98% of people age 65 years and older have at least two chronic diseases and take at least five prescription medications.[93]

As the medical field develops clinical therapies, protocols, and treatments to help the elderly population better manage, prevent, and/or enhance quality of life, there are also risks. For instance, polypharmacy—taking multiple medications concurrently—and the use of potentially inappropriate medicines (PIMs) pose the greatest risk of drug-related adverse events (ADEs) for older adults, who are more likely than younger people to take multiple medications at the same time.[94] Broadly defined as injuries that result from drug-related medical interventions (e.g., medication errors, adverse drug reactions, allergic reactions, or overdoses), ADEs have been associated with thousands of visits to the emergency department (ED) and hospitalizations. However, up to half of identified ADEs are preventable, and ADEs are one of the most common types of preventable adverse events across all healthcare settings. Common consequences of ADEs include drug-related morbidity and mortality, heart and/or renal failure, gastrointestinal and internal bleeding, and negative drug-drug interactions.

Polypharmacy and the use of inappropriate medications present a risk for ADEs. Driven by the need to identify the most precise way to identify ineffective and/or unnecessary medications, several intervention strategies report varied success in implementation and effectiveness. This section focuses on two emerging approaches: (1) deprescribing to reduce polypharmacy and (2) the use of the Screening Tool of Older Person's inappropriate Prescriptions (STOPP) criteria to reduce PIMs. Deprescribing involves reducing doses or stopping medications that are not useful or are no longer needed in order to reduce polypharmacy, reduce harm, and improve health. STOPP is a validated, evidence-based list of 80 criteria for potentially inappropriate prescribing in older adults, first published in 2008 and revised in 2014.

While it is a fairly new tool, evidence suggests that STOPP may be better at predicting PIMs in older adults than other tools, such as the American Geriatrics Society's Beers Criteria, hereafter referred to as the Beers Criteria. While this patient safety practice (PSP) specifically emphasizes the use of the STOPP criteria, it is often used with a companion screener, the Screening Tool to Alert to Right Treatment (START). START includes a set of 34 evidence-based and validated prescribing indicators for common diseases for the same population. Both have been more commonly used in non-U.S. settings.

Deprescribing

As previously discussed, deprescribing addresses polypharmacy by reducing inappropriate prescriptions and can lead to improved clinical outcomes. However, clinical outcomes can vary with the specific approach to deprescribing. Ocampo et al. (2015) found that a pharmacist-led medication review with an 18-month follow-up period in community pharmacies identified 408 negative outcomes related to prescriptions and resolved 393 of these problems, resulting in a significant decrease in hospitalizations and ED visits.[95] Physical and mental health summary scales increased from 65.8 to 82.7 and 66 to 81, respectively, while patients who were nonadherent decreased from 68 to 1.

Others reported that discontinuing multiple medications simultaneously was significantly associated with reductions in both the number of reported falls and frailty scores for older adults.[96] These researchers also examined collaborative medication reviews with general practitioners of patients age 65 years and older in a residential care facility. Their study noted a significant reduction in drug burden index scores, reflecting a decrease in the cumulative exposure to medications, and the number of falls and frailty measured using the Edmonton frailty scale dropped by a mean difference of 1.35 ($p<0.05$). Additionally, the number of adverse drug reactions decreased by 4.24 ($p<0.05$) after 6 months.

Protocols, algorithms, and clinical decision support systems

Patients had a significant decrease in the number of medications prescribed in studies focusing on the use of protocols, algorithms, and clinical decision support systems to promote deprescribing. A patient-centered deprescribing protocol called Shed-MEDS is implemented in four phases: (1) confirm medication history and list, (2) evaluate medication for deprescribing, (3) decide with the patients, (4) synthesize and communicate recommendations. Petersen et al. (2018) found that, among Medicare beneficiaries prescribed five or more medications, the mean number of prescribed medications was significantly reduced, from 11.6 to 9.1 ($p=0.032$), for those receiving the protocol.[97]

McKean et al. (2016) worked with patients age 65 or older taking eight or more medications to implement an intervention consisting of a formal medication review among rounding clinicians, followed by receipt of a paper-based or computerized form listing clinical and medication data linked with a five-step clinical decision support tool to determine drugs eligible for discontinuation.[98] The intervention led to a 34% decrease in regular medications, a small but nonsignificant decrease in PRN (as needed) medications, and a significant decrease in the number of medications per patient at discharge compared with admission.

Education-improvement interventions, which directly educate consumers, have also been associated with medication discontinuation to reduce polypharmacy. Tannenbaum et al. (2014) found that a direct- to-consumer education intervention using an 8-page booklet to describe the risks of benzodiazepine use and a step-wise tapering protocol led to a 27% discontinuation of benzodiazepines among community pharmacy patients age 65 or older in the intervention group, compared with 5% in the control group 6 months after the intervention.[99] A consumer-based education intervention led by pharmacists in community pharmacies providing an educational brochure to patients age 65 and older resulted in 43% of the intervention group no longer filling inappropriate medications, compared with 12% of the control group.[100]

Pharmacist or clinician–led medication reviews

Pharmacist-led medication review interventions across a number of settings have also promoted deprescribing. Lenander et al. (2014) found that a pharmacist-led medication review in a primary care setting targeting patients 65 and older with five or more different medications led to a decrease in drug-related problems.[101] Using the Beers Criteria, after 12 months, drug-related problems decreased for the intervention group from 1.73 to 1.31 ($p<0.05$). There was also a larger reduction in the number of drugs prescribed in the intervention group ($p<0.046$).

Medication reviews involving both pharmacists and clinicians can effectively decrease medication use. Chan and others (2014) determined the effectiveness of a medications safety review clinic for geriatric outpatients age 65 or older who were prescribed eight or more chronic medications or who had visited at least three different physicians at the two participating hospitals within 3 months. Four medication review sessions were performed by two research assistants, one clinical pharmacist, and one geriatrician, leading to a mean decrease in chronic medications from 9.0 to 8.6 ($p<0.05$).[102]

Key findings

- Geriatrician and clinical pharmacist reviews can effectively reduce the use of unnecessary medications.
- Educating patients and their families helps them better communicate their medication use to providers in order to discontinue unnecessary medications.
- Deprescribing reduces medication- related costs for patients and healthcare systems.

Using the STOPP criteria

Several studies demonstrate the effectiveness of STOPP. Campins et al. (2017) reported that the STOPP tool helped pharmacists determine that 27% of the intervention population's prescriptions were potentially inappropriate.[103] The majority of these prescriptions were then changed, as follows: 43% were discontinued, 33% received a dose adjustment, 14% were substituted for more appropriate medications, and for 10%, the patient received a new prescription.

Similarly, Gibert et al. (2018) used STOPP in primary care consultations in France, resulting in a 38% reduction in the number of PIMs across about 45% of patients.[104] Hannou et al.(2017) introduced a part-time ward-based clinical pharmacist to a psychiatric unit's multidisciplinary team and screened prescriptions for potentially inappropriate drug prescribing (PIDP) using the STOPP/START criteria.[105] The intervention was measured by the acceptance rate of pharmacist interventions (PhIs). The global PhI acceptance rate was 68% and the rate based on STOPP/START was 47%. When two STOPP criteria, the prescription of benzodiazepines or of neuroleptic drugs to patients who had fallen in the last 3 months, were removed from analysis, the acceptance rate for STOPP/START-based PhIs increased to 67%.

One potential unfavorable effect of deprescribing interventions is that, while the interventions have reduced medication costs, they do not always lead to a decrease in healthcare utilization, such as hospital admissions and primary care visits. With the exception of longer lengths of stay no other unintended negative consequences were reported in the studies that examined the use of STOPP criteria to reduce ADEs.

Barriers to deprescribing

In the deprescribing literature, notable barriers to implementation included:[100]

- Pharmacists not adhering to study protocols
- Inadequate documentation of medication history
- Limited communication between pharmacists and physicians
- Patients being discouraged from discontinuing medications by individual providers
- Patients perceiving deprescribing as contradicting their provider's recommendations
- Scheduling conflicts, competing demands, and general lack of time, which impacted medication review meetings between pharmacists and physicians
- Nonprescription medications (i.e., over-the-counter) that were not documented in medical databases, which prevented providers from seeing the full-range of medication use per patient and therefore not being able to accurately identify and include all patients who were at risk of polypharmacy in the study
- Lower acceptance rates of pharmacist interventions based on the STOPP criteria due to the lack of discontinuation of benzodiazepines

Conclusions

Being able to prevent unnecessary ADEs that are associated with the use of inappropriate medication use or polypharmacy is especially important for older adults who are affected by multiple ailments and who inevitably traverse multiple healthcare settings and providers for treatment. Deprescribing to reduce polypharmacy and use of the STOPP criteria to reduce PIMS are two approaches to consider. Albeit still emerging, studies on deprescribing highlight its potential in helping providers adjust down and/or eliminate medications based on the condition/need of patients. However, more research is needed to assess deprescribing in relation to patient adherence, compliance, and preference, as patients play a key role in a provider's ability to effectively monitor and adjust medication and treatment plans.

With regard to using the STOPP criteria to reduce PIMS, evidence suggests it is the most effective approach, but also note that it often does not—and should not—stand alone. In order to ensure thatolder adults are given the best possible care, in addition to screening their prescriptions for PIMS (i.e., using STOPP), it is equally important to identify more appropriate treatment options, thus also including the START criteria. More appropriate medication selection is also achieved through the use of the Beers Criteria or the Medical Appropriateness Index (MAI), which are other interventions that oftenaccompany the use of STOPP.

The field will undoubtedly benefit from more studies that examine the short- and long-term clinical effects of reducing polypharmacy and PIMS through deprescribing and using the STOPP criteria.

Harms due to opioids

The United States has seen three successive waves of opioid overdose deaths related to both legal and illegal opioids.[106] The first began in the 1990s and was associated with steadily rising rates of prescription opioids. In 2010, deaths from heroin increased sharply, and by 2011 opioid overdose deaths reached "epidemic" levels as described by the Centers for Disease Control and Prevention (CDC).[107] The third wave began in 2013 with a sharp rise in overdose deaths attributed to synthetic opioids, particularly those involving illicitly-manufactured fentanyl.

In late 2020, the CDC announced that 81,230 drug overdose deaths occurred in the 12 months ending in May, 2020, which was the highest level of overdose deaths ever reported.[108] The surge was primarily driven by a 34% increase in overdose deaths related to synthetic opioids, primarily fentanyl.[108] Overdose rates appear to have accelerated during the COVID-19 pandemic.[109] Between 1999 and 2019, the CDC estimates that nearly 500,000 people in the United States died from such overdoses.[110]

This section reviews two PSPs that aim to mitigate the potential harms of opioids: opioid stewardship and initiation of Medication Assisted Treatment (MAT) for opioid use disorder (OUD) Opioid stewardship can consist of a range of risk-reduction interventions or strategies often used in combination. Evidence is moderately strong that opioid stewardship interventions can reduce opioid dosages, which is an important intermediate outcome given high MMEs are associated with an increased risk of overdose.

MAT can be initiated and provided safely in a variety of healthcare settings. Initiation of MAT in the ED, primary care setting, or outpatient clinics may result in faster access to care and longer retention in or adherence to treatment. MAT's effectiveness in reducing illicit opioid use and overdose deaths has already been demonstrated in multiple randomized clinical trials, and effective MAT includes a combination of behavioral therapy and medications approved by the Food and Drug Administration (methadone, buprenorphine, and naltrexone).

Opioid stewardship

Opioid stewardship—similar to antibiotic stewardship—consists of a range of risk-reduction interventions or strategies, often used in combination, to prevent adverse consequences from prescription opioids, including misuse, abuse, and overdose. The range of opioid stewardship interventions or strategies includes the following, several of which are recommended in the Centers for Disease Control and Prevention's Guideline for Prescribing Opioids for Chronic Pain:[111]

- Conduct of an individualized assessment of risks and benefits of opioids, and the appropriateness of a tapering (tapering slowly to minimize withdrawal symptoms)
- Avoid coprescribing opioids and benzodiazepines or other sedative hypnotics (as appropriate)
- Use of treatment agreements (also known as controlled substance agreements or pain contracts)
- Urine drug screening (UDS)
- Checking Prescription Drug Monitoring Programs (PDMPs)
- Pain and functional assessment.
- Registry of patients with chronic pain or patients on chronic opioid therapy (COT)
- Limiting number of days supply for acute pain opioid prescriptions
- Pill counts to detect aberrant drug-related behavior
- Referrals to nonpharmacologic treatment providers (e.g., physical therapy), pain management, behavioral health, or addiction specialists
- Risk assessment

Besides recommending these specific interventions, most opioid stewardship initiatives also include implementation strategies to actually change practice. These implementation strategies are not necessarily unique to opioid stewardship efforts and include electronic health record (EHR) tools (e.g., clinical decision support, templates, alerts, integrated PDMP, autopopulated fields), dashboards for monitoring and/or audit and feedback, provider and staff education and training, academic detailing, committee or task force on opioids, telehealth, and nurse care management.

Most opioid stewardship initiatives are multicomponent interventions, involving clinical interventions or care processes and often implementation strategies as well. The implementation strategies included education, policies, dashboards, audit and feedback, monitoring and metrics, health information exchange, and EHR tools. The EHR tools included an embedded PDMP, registry, alerts, autopopulation features, and templates.

Weiner et al. (2019) found that it is critical to determine metrics and gain access to data at the beginning in order to guide the opioid stewardship effort.[112] They also experienced a mismatch when primary care providers referred patients to pain specialists with the expectation that the pain physicians would prescribe opioids, whereas the specialists would only recommend opioid regimens and provide injections. Additionally, while their health system had increased access to substance use disorder treatment, their outpatient practices perceived there was inadequate access. Finally, they learned that many of these implementation challenges could be addressed by convening the various stakeholders to resolve the issues. Buy-in and administrative support were identified as key for two opioid stewardship initiatives, also.

It should be noted that while most opioid stewardship efforts are aimed at preventing or reducing harms due to opioids with appropriate prescribing, the stewardship efforts could also result in unintended negative consequences, such as patients having poorly controlled pain, experiencing the negative consequences of forced tapers, or turning to illicit opioids.

Medication-Assisted Treatment

MAT is a proven method to treat OUDs. Effective MAT includes a combination of behavioral therapy and medications approved by the Food and Drug Administration (methadone, buprenorphine, and naltrexone). Individuals with OUD can safely take medications used in MAT as part of a long-term recovery plan.

This section focuses on initiation of MAT, as MAT's effectiveness in reducing illicit opioid use and overdose deaths has already been demonstrated in multiple randomized clinical trials.[113]

Initiation of MAT can occur in primary care offices, EDs, hospitals, and community-based centers and clinics. The setting of MAT initiation might impact process and clinical outcomes, including engagement in and adherence to the patient's treatment and recovery plan. Initiation usually refers to the first prescription of a medication, as the psychosocial aspects of the treatment are not available in every setting (e.g., hospital) in which the prescriptions can be given.

The maintenance phase of treatment occurs when a patient is doing well on a stable dose of MAT medication, without side effects, cravings, or problematic use. Patients achieve the maintenance phase at different lengths of time following medication initiation. A patient may remain in the maintenance phase on the same dose of medication indefinitely or may choose to taper off of the medication.

Evidence suggests advantages to maintenance therapy as opposed to tapering MAT medications. Specifically, maintenance treatment was associated with less use of illicit opioids, as measured by urine drug tests (UDTs), as opposed to tapering off the medication after stabilization was achieved.

For example, Liebschutz et al. (2014) conducted an RCT of 139 hospitalized opioid-dependent patients in the general medical units of one urban safety-net hospital between 2009 and 2012.[114] Patients were randomized to receive either transition to hospital-based outpatient buprenorphine treatment upon discharge or to receive a 5-day buprenorphine taper, which was continued at home if discharge occurred before finishing the taper. At 6-month follow-up, participants who received linkage to outpatient treatment were more likely to enter outpatient buprenorphine treatment (72.2% vs. 11.9%; $p<0.001$); were more likely to remain in treatment (16.7% vs. 3%]; $p=0.007$); and were less likely to report illicit opioid use in the past month.

Results have generally been mixed regarding the benefit to clinical outcomes of adding psychosocial interventions to MAT, which generally involved some form of individual or group psychotherapy using a modality such as cognitive behavioral therapy (CBT), Acceptance and Commitment Therapy (ACT), or motivational interviewing.

Key findings about MAT

- MAT can be initiated and provided safely in a variety of healthcare settings
- It has been most studied in primary care settings, hospitals, EDs, and community-based centers and clinics— for example, HIV/AIDS clinics
- Initiation of MAT in the ED, primary care setting or outpatient clinics may result in faster access to care and longer retention in or adherence to treatment
- The majority of the studies found through the searches of the literature had sample sizes too small to detect differences between treatment groups—for example, RCTs with limited power to detect differences. Additionally, many of the studies' follow-up periods were relatively short—for example, less than 6 months.

Delirium

Patient safety research and quality improvement efforts have been underway in the delirium harm area for many years, but clear and consistent recommendations regarding best practices have proven elusive. Studies have been conducted, including rigorously designed systematic reviews, but they have reached conclusions that have been contradictory and difficult to apply across settings.

A 2019 systematic review that focused on the effectiveness of nonpharmacological interventions in reducing the incidence and duration of delirium in critically ill patients concluded that "current evidence does not support the use of non-pharmacological interventions in reducing incidence and duration of delirium in critically ill patients" and recommended further research with clearly defined outcomes.[115] A 2019 Cochrane systematic review that targeted older adults in institutional long-term care (LTC) found only limited evidence on interventions for preventing delirium in the LTC setting.[116]

In recent systematic reviews examining antipsychotics for treating and preventing delirium in hospitalized adults, researchers found that current evidence does not support routine use of haloperidol or second-generation antipsychotics for prevention or treatment of delirium.[117] There is limited evidence that second- generation antipsychotics may lower the incidence of delirium in postoperative patients, but more research is needed.

This section discusses three patient safety practices focused on delirium: use of screening and assessment tools for recognition of patients with delirium; training and education of staff to recognize signs and symptoms of delirium; and nonpharmacological interventions aimed at prevention or reduction of delirium among critically ill patients in intensive care.

Background

Delirium is the term used to refer to an acute decline in attention and cognition that constitutes a serious problem for older hospitalized patients and many residents in LTC facilities. Precipitating risk factors for delirium include acute illness, surgery, pain, dehydration, sepsis, electrolyte disturbance, urinary retention, fecal impaction, and exposure to high-risk medications. It is the most common complication among hospitalized individuals 65 years and over.

Delirium in older hospitalized patients ranges from 14 to 56%, with hospital mortality rates ranging from 25 to 33 percent. Adults over 65 years of age account for 48 percent of all delirium-associated hospital days.[118] Delirium is associated with increased mortality, postoperative complications, longer lengths of stay, functional decline, and significant financial costs. One study estimated that delirium is unrecognized in about 60 percent of all cases.[119] This statistic is particularly troubling, as early detection of delirium has been demonstrated to improve health outcomes. However, to recognize delirium, it is necessary to know the older adult's baseline health status so that any changes—which can occur within hours—can be quickly identified. Therefore, older adults should be assessed frequently using standardized tools so that up-to-date baseline information is readily available. Further, appropriate training and education for staff in recognizing and treating delirium should be provided.

With a longstanding and still-growing body of evidence pointing to significant health and financial impacts of delirium on hospitalization and other healthcare costs, it is clear that individuals at risk for delirium should be identified as quickly as possible and preventive strategies should be implemented early in an encounter with the healthcare system.

Affected individuals should be followed after discharge to mitigate any long-term effects of delirium after a hospital stay or other medical treatment.

Focusing patient safety efforts on delirium is appropriate, given that the problem is common and associated with serious complications, and is increasing in magnitude as the population ages. Delirium may be preventable in certain circumstances—with some estimates finding delirium preventable in 30 to 40% of cases—thereby increasing quality and safety of care, as well as reducing costs to the healthcare system.[120] Awareness of these costs can drive improvement in screening and assessment of individuals at risk for onset of delirium, and in further study of treatment strategies that both reduce costs of care and improve quality of life. Healthcare professionals need adequate training and education to be vigilant and effective in assessing their patients for delirium in all healthcare settings.

Delirium screening and assessment

Delirium, a clinical diagnosis, is often unrecognized and easily overlooked. Recognition requires brief cognitive screening and astute clinical observation. Key diagnostic features include an acute onset and fluctuating course of symptoms, inattention, impaired level of consciousness, and disturbance of cognition (e.g., disorientation, memory impairment, alteration in language). Supportive features include disturbance in sleep-wake cycle, perceptual disturbances (hallucinations or illusions), delusions, psychomotor disturbance (hypo- or hyper-activity), inappropriate behavior, and emotional lability.

There is no widely accepted pharmacological means of preventing delirium in the at-risk population over 65 years of age. Consequently, multicomponent approaches for primary prevention of delirium have gained widespread acceptance as the most effective strategies for addressing delirium.

While a single factor may put a patient at high risk for developing delirium, it is more likely that a combination of risk factors, including multimorbidity, dementia, certain medications, and isolation, place an individual at a much higher risk, especially if he or she is over 65 years of age. The leading risk factors of delirium consistently reported at hospital admission are dementia or cognitive impairment, functional impairment, vision impairment, history of alcohol abuse, and advanced age (> 70 years). Comorbidity burden or presence of specific comorbidities (e.g., stroke, depression) are associated with an increased risk of delirium in all patient populations.

Nonpharmacological interventions

Nonpharmacological interventions aimed at prevention orreduction of delirium fall into several domains, including mobility (early mobilization, physical, occupational therapy), environmental (noise reduction, music, light adjustment, ear plugs, eye shades, avoidance of physical restraints), cognitive (reorientation, cognitive activities), and therapeutic (sleep promotion, attention to hearing or vision deficits, nutrition and hydration, minimization of indwelling urinary catheter use).

Results related to effectiveness of nonpharmacological interventions are mixed. Nonpharmacological interventions significantly reduced delirium incidence in four trials, while two reported nonsignificant results and one a nonsignificant increase. Statistically significant reduction in duration of delirium was reported in four studies.

Studies have shown multicomponent nonpharmacological interventions to be effective for reduction of delirium among intensive care patients, although the quality of the evidence is low to moderate. Reproducibility and scalability are hindered by a lack of evidence regarding which components of many are requiredto achieve the desired effect. In addition, specific details of implementation required for replication and level of adherence to protocols arenot often reported.

Conclusions about delirium

Given the importance of delirium as a harm area in many healthcare settings, additional research appears necessary. The results of this review highlight the need for evidence-based tools that can be readily used by frontline caregivers to reliably assess and re-assess patients for signs/symptoms of delirium, whether they are in acute care or in a variety of post-acute care settings.

Early identification of delirium and the application of best practices to reduce harm with these populations at risk for delirium are crucial to maintaining patients' functional capabilities and improving their safety in the healthcare system. The literature is clear that unrecognized, untreated delirium leads to adverse events such as falls, polypharmacy, restraints, and readmissions. Studies found that the Confusion Assessment Method (CAM) or one of its variations and associated tools was reliable in identifying delirium patients. New tools should also be evaluated as they are developed, again especially in settings other than acute care. Attention will have to be given to how long it takes to assess patients using these tools and the ability of clinicians to accurately use them. Additional time may be needed for ongoing training and evaluation of competence in using methodsand tools specific to a particular institution.

There is clearly an ongoing need for inclusion of delirium as an important patient safety topic in the education and training of clinicians and other providers including nurses, physicians, pharmacists, and social workers, especially as our population continues to rapidly age.

Care transitions

As patients prepare to move from the hospital to other settings, failing to make adequate discharge arrangements can lead to costly and unnecessary hospital readmissions, preventable adverse events, and drug-related errors. Ensuring safe and seamless transitions starts well before hospital discharge. Successful transitioning of patients from the hospital to other care settings is a dynamic, multifaceted process in which healthcare systems, hospitals, providers, patients, and their families share responsibility. Models or interventions such as Better Outcomes for Older Adults (BOOST), the Care Transitions Intervention (CTI), and the Transitional Care Model (TCM) were developed with the intention of improving transitions across the continuum of care. These models appear to be especially beneficial for high-risk and older adult populations, who are often hospitalized; move frequently across care settings; and experience high rates of post-discharge complications, readmissions, or morbidity and mortality.

Transitioning patients from one setting to another is a particularly vulnerable time. Safety lapses can result in negative clinical outcomes, preventable adverse events, and avoidable hospital readmissions. The following seven key elements are considered essential for safe and seamless transitions:

- Medication Management: Ensuring the safe use of medications by patients and their families based on patients' plans of care.
- Transition Planning: Creating a plan/process that facilitates the safe transition of patients from one level of care to another, including home or from one practitioner to another.
- Patient/Family Engagement and Education: Educating and counseling patients and families to enhance their active participation in their own care, including informed decision making.
- Communicating and Transferring Information: Sharing of important care information among patient, family, caregiver, and healthcare providers in a timely and effective manner.
- Follow-Up Care: Facilitating the safe transition of patients from one level of care or provider to another through effective follow-up care activities.
- Healthcare Provider Engagement: Demonstrating ownership, responsibility, and accountability for the care of the patient and family/caregiver at all times.
- Shared Accountability Across Providers and Organizations: Enhancing the transition of care process through accountability for care of the patient by both the healthcare provider (or organization) transitioning, and the one receiving the patient.

BOOST: Better Outcomes by Optimizing Safe Transitions

Project BOOST is a multicentered quality improvement (QI) transitional care program created in 2008 by the Society of Hospital Medicine to improve care for patients as they transition from the hospital to home.[121] The objective is to reduce 30-day readmission rates, improve provider workflow, and reduce medication-related errors. The model involves tools and resources to identify and manage patients at high risk for readmissions, with a particular focus on older adults.

When hospitals adopt this model they can tailor components to align with their unique needs, priorities,available resources, and culture. There is a toolkit that includes resources to address areas of the discharge process that are predisposed to result in adverse events. Implementation outcomes (e.g., organizational change, reduced hospital readmissions) are estimated for 12 and 24 months post- discharge. After the model is adopted, the hospital becomes part of a QI collaborative network through which they can communicate with and learn from other BOOST members around the country. Additionally, a BOOST Data Center allows users to store and benchmark data against control units andother providers.

BOOST is intended for use by all clinicians involved in the hospital discharge process (physicians, nurses, case managers, social workers), with a core team consisting of a team leader (nurse, case manager, social worker, or physician), QI facilitator, project manager, process owners (frontline staff involved in providing safe, effective care transitions in the hospital, including pharmacy, nursing, and case management staff), and information technology experts.

- The BOOST toolkit:
- Participant Implementation Guidance
- Patient Risk Assessment
- Universal Patient Discharge Checklist
- General Assessment of Preparedness
- The Patient Preparation to Address Situations Successfully
- Discharge Patient Education
- Teach Back Curriculum
- Discharge Instructions for Providers
- Guidance for a 72-Hour Post- Discharge Follow-Up Call andAppointment
- General Guidance for MedicationReconciliation

In 2013, Hansen et al. evaluated the effect of BOOST on Medicare beneficiaries' readmission rates and length of stay in a sample of 11 hospitals of varying size, academic affiliation, and location.[121] They found that BOOST was associated with a 3% decrease in 30-day readmissions (p=.010) after 12 months of implementation. The length of stay did not change significantly.

CTI: Care Transitions Intervention

Dr. Eric Coleman developed the Care Transitions Intervention in 2002 to improve continuity of care across care settings and providers. CTI is a patient-centered, multi-component program that has since been implemented in hospitals across the country.[122] Developed based on input from patients and their caregivers, CTI aims to improve the efficiency and quality of care in the transition from hospital to home by providing patients with tools and support to navigate the healthcare system and effectively manage their health conditions.

CTI is a 4-week, low-cost, low-intensity self-management program designed to provide patients discharged from an acute care setting with skills, tools, and the support of a transition coach to ensure that their health and self- management needs are met. The intervention targets patients age 65 years and older, who often have acute or chronic health conditions such as congestive heart failure, chronic pulmonary disease, diabetes, stroke, hip fractures, pulmonary embolism, and deep vein thrombosis.

CTI begins when the patient is in the hospital. A Transitions Coach sets up a meeting to discuss the patient's concerns and to engage the patient and family to begin participating in the program. Next, the Transitions Coach conducts a follow-up home visit and a series of three phone calls in order to help the patient increase self-management skills and attain personal goals, and to provide the patient and his or her family continuity across the transition. Transition coaches can be advanced practice nurses (APNs), registered nurses, social workers, student nurses, community workers, or trained volunteers.

CTI's Four Pillars of Care:

- Medication Self-Management: Patient/ caregiver is knowledgeable about prescribed medication(s) and establishes a medication management process.
- Dynamic Patient-Centered Health Record: Patient (with assistance from caregiver, if necessary) uses the Personal Health Record to communicate with and consult about continuity-of-care providers from across different settings.
- Primary Care and Specialist Follow-Up: Patient schedules and completes follow-up visits with the providers (i.e., primary care provider or specialist) and is empowered to actively participant throughout.
- Knowledge of Red Flags: Patients understand indicators for when their condition is worsening and know how to respond.

TCM: Transitional Care Model

Developed in 1981 at the University of Pennsylvania's School of Nursing by a team led by Dr. Mary Naylor, the Transitional Care Model[123] is a nurse-led intervention designed to improve the outcomes of chronically ill older adults who transition from hospital to home and are at risk of readmission based on the following factors:

- One or more chronic illnesses
- More than one hospital visit within the last 6 months
- Multiple prescribed medications to treat multiple conditions (i.e., polypharmacy)
- Living alone

The model is implemented through the use of individualized, multidisciplinary, evidence-based clinical protocols that help to prevent declines in health and to reduce 30–60 day hospital readmissions. In addition to reducing rates of readmissions, TCM also aims to enable patients and their family caregivers to manage their conditions themselves. Although originally designed for older adults at risk of readmission, the model has been recently adapted and tested with other populations, including individuals who are eligible for Medicaid and patients with psychiatric diagnoses in addition to chronic and other comorbidities.

Patients who fit the criteria for the intervention meet with an advanced practice nurse either in the hospital prior to discharge or within 48 hours after discharge. The APN conducts home visits and telephone support, and is available 7 days a week through the length of the intervention (usually extending for 2 months after discharge). The APN uses the initial visit to assess the patient and develop a plan of care based on medical needs and patient values. Subsequently, the APN focuses on active engagement and education of patients and family caregivers. APNs educate patients about their health conditions and risks, including how to recognize and manage symptoms of worsening. They use home visits to monitor symptoms and do medication reconciliation. APNs serve as liaisons between patients/family caregivers and healthcare providers to ensure that follow-up visits are scheduled with primary or specialist providers after discharge from the hospital. APNs are available to accompany patients to these follow up visits, if requested.

Key findings related to transitions of care

Moving patients from one care setting to another can pose significant risk. Implementing transitional care models such as BOOST, CTI, and TCM, which place an emphasis on medication management, transition planning, patient/family engagement and education, communication and transferring information, follow-up care, healthcare provider engagement, and shared accountability across providers and organizations, is a patient safety practice that appears to have great potential. Evidence shows that implementing these models results in standardization in discharge protocol, ultimately leading to a decrease in hospital readmissions and an increase in associated cost savings. However, more diverse studies using these models are needed to establish a firm evidence base in a variety of care settings.

Studies focusing on model implementation in a variety of care settings, including rural hospitals, patient-centered medical homes, accountable care organizations, and community-based palliative care programs, would lead to stronger clinical evidence and improved implementation. Existing studies primarily focus on Medicare populations in large urban academic medical centers. Future research on implementation of these models in a variety of settings with diverse patient populations is critical for understanding opportunities and outcomes associated with multi-element models designed to improve transitional care.

Venous thromboembolism

Venous thromboembolism (VTE) is a disorder that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). A DVT occurs when a blood clot forms in a deep vein, usually in the lower leg, thigh, or pelvis. A PE occurs when a clot breaks loose and travels through the bloodstream to the lungs.

It is estimated that 300,000 to 600,000 Americans are affected each year by VTE, making it the third leading vascular diagnosis behind heart attack and stroke, and the leading cause of death due to major orthopedic surgery. Common causes for VTE are surgery, cancer, immobilization, or hospitalization. The risk of VTE is the highest for patients undergoing major orthopedic surgery, such as total knee arthroplasty (TKA), total hip arthroplasty (THA), or hip fracture surgery (HFS). Without appropriate prophylaxis, rates of VTE among these patients have been estimated to be as high as 60%.[124] Given that major orthopedic surgeries typically occur among older adults, the Centers for Medicare & Medicaid Services (CMS) has made the prevention and treatment of VTE a priority among their quality improvement efforts, such as through programmatic measure inclusion and harm area prioritization in initiatives. Accreditation organizations have followed suit, with the Joint Commission and the National Committee for Quality Assurance including measures for VTE treatment and prevention in their hospital accreditation and certification programs.

Aspirin for VTE prophylaxis

As VTE, in particular DVT, can be very difficult to diagnose, actively employing prevention techniques is critical to ensuring patient safety. Prevention methods include both mechanical and pharmacologic prophylaxis. Mechanical prophylaxis includes the use of compression devices, such as stockings and foot pumps. Pharmacologic prophylaxis is available via a number of different anticoagulant and antiplatelet drugs, including heparin derivatives, vitamin K antagonists, direct thrombin inhibitors, direct factor Xa inhibitors, and aspirin.

There are two different types of pharmacologic agents available for VTE prophylaxis—anticoagulants and antiplatelets. Aspirin is an antiplatelet, and while there are other antiplatelets used for other cardiovascular conditions, these are not recommended for use in VTE prophylaxis. There is slight variation in existing guidelines regarding the use of aspirin for pharmacologic prophylaxis. The American Society of Hematology (ASH) the American College of Chest Physicians (ACCP), and the American Academy of Orthopedic Surgeons (AAOS) all recommend pharmacologic prophylaxis and/or mechanical prophylaxis for patients undergoing THA, TKA, or HFS. ASH and AAOS further recommend that patients receive both forms of prophylaxis, particularly patients who are at an increased risk for VTE. However, ASH and ACCP provide a list of recommended pharmacologic agents that specifically includes aspirin, whereas AAOS does not make recommendations regarding specific pharmacologic agents. Further, ACCP recommends low molecular weight heparin (LMWH) over other pharmacologic prophylaxis agents, whereas other guidelines have not made such a specific recommendation statement specifying the use of one type of pharmacologic prophylaxis agent over another.

Many hospitals include the use of aspirin in their surgical protocols for patients undergoing major orthopedic surgery. For prescribing surgeons, its use is at their discretion based on guideline recommendations, perceived patient risk, and the need to balance prevention with safety concerns, such as bleeding risk. This balance has become increasingly important as a growing number of studies have found that newer anticoagulant drugs are associated with a higher incidence of bleeding than prophylaxis agents.

Aspirin as sole prophylaxis treatment

In a comprehensive analysis of available pharmacologic prophylaxis options, Agaba et al. (2017) conducted a retrospective review of patients undergoing THA using a nationwide private and Medicare insurance database.[125] Patients studied received either aspirin alone or one of five anticoagulants. The analysis found that patients given aspirin alone had a significantly lower rate of both DVT and PE at 30 and 90 days following surgery, with an insignificant bleeding risk. Following a review of the effectiveness and safety side effects of each of the pharmacologic agents included in the study, the authors concluded that while rivaroxaban and fondaparinux have lower bleeding and thromboembolic events compared with other newer anticoagulants, aspirin also meets these criteria. In addition, aspirin is an easy-to-use, inexpensive option for prophylaxis following THA.

Aspirin combined with other pharmacologic prophylaxis

Several studies address the use of aspirin in combination with other pharmacologic prophylactic agents. For example, Anderson et al. (2018) conducted a double-blind randomized controlled trial at 15 university-affiliated health centers in Canada.[126] Patients undergoing elective unilateral primary or revision hip or knee arthroplasty received once-daily oral rivaroxaban for the first 5 days following surgery, and then were randomized to either continue the course of rivaroxaban or switch to aspirin for the next 9 days after TKA, or 30 days after THA. Findings indicate that aspirin is not worse ($p<0.001$) but not better than continued use of rivaroxaban. Additionally, there was not a significant difference in bleeding between the two groups ($p=0.43$).

Hamilton et al. (2012) conducted a retrospective review of patients receiving aspirin prophylaxis after primary hip and knee arthroplasties.[127] Patients received a course of enoxaparin during their inpatient stay, followed by a course of aspirin for 28 days following discharge. Patients were compared with a control group that first received enoxaparin for 2 weeks following discharge before receiving a course of aspirin for a further 2 weeks. Researchers concluded that a protocol of only inpatient enoxaparin and then aspirin post discharge was both safe and effective in standard-risk patients.

Aspirin combined with mechanical prophylaxis

Many studies have evaluated the use of an anticoagulant or antiplatelet in combination with other mechanical prophylaxis methods and most conclude that aspirin is safe and effective when used this way. For example, Deirmengian et al. (2016) conducted a retrospective review of patients undergoing TJA.[128] All patients received mechanical prophylaxis and then either warfarin ($n=2463$) or aspirin ($n=534$). The study found that the differences between the groups with regard to DVT or PE alone were not statistically significant ($p=0.15$; $p=0.06$, respectively). Fisher's exact test showed a significantly higher risk for any symptomatic VTE in patients receiving warfarin (43 events, 1.75%) compared with patients receiving aspirin (3 events, $p=0.03$).

Aspirin dosing considerations

In their retrospective analysis, Faour et al. (2018) analyzed the medical records of patients receiving aspirin twice daily for 4 to 6 weeks following TKA.[129] Patients received low-dose, 81 mg, aspirin ($n=1,327$) or standard-dose, 325 mg ($n=2,903$). Analysis concluded that aspirin is safe and effective but that there was a significant difference in the incidence of VTE and DVT between the two groups ($p=0.02$ and $p<0.001$, respectively), with those receiving a standard dose experiencing a higher incidence of VTE and DVT (1.5% vs. 0.7% and 1.4% vs. 0.3%). However, there was not a significant difference in the incidence of PE ($p=0.13$), and a regression analysis showed no correlation between aspirin doses and the incidence of VTE (both DVT and PE) or DVT alone ($p=0.94$ and 0.20). Further, there is no statistically significant difference in the incidence of gastrointestinal (GI) or wound bleeding ($p=0.62$). Faour et al. reached similar conclusions when conducting the same retrospective analysis for patients undergoing THA.

Unintended consequences

There are a number of potential unintended consequences associated with the use of aspirin for VTE prophylaxis. Generic aspirin is widely available and significantly cheaper than alternative medications. Additionally, administrative costs are lower than with some alternative pharmacologic prophylaxis agents that require intravenous delivery or ongoing laboratory monitoring, such as with warfarin. Ease of administration may in turn have a positive impact on patient quality of life during the treatment period and support medication adherence.

As with other pharmacologic prophylaxis agents, there is the potential risk that patients prescribed aspirin following major orthopedic surgery will experience operative site or major bleeding. The analysis of the incidence of these events was a priority for many of the articles included in this review. Twenty- three of the studies specifically addressed unintended patient safety outcomes in their analysis and conclusions. Of those, 22 concluded that overall aspirin was safer than other pharmacologic options, or had comparable risk.

The identified systematic reviews reached similar conclusions, with two of the reviews determining that use of aspirin has a lower bleeding relative risk than other pharmacologic options. Other studies found no difference in bleeding risk between aspirin and other therapies.

Implementation

An important consideration when establishing the appropriateness and potential efficacy of aspirin following major orthopedic surgery is the patient risk profile. While 24 of the 27 included studies

determined aspirin is safe and as effective, if not more effective, than other prophylaxis methods, a potential confounding or even misleading factor is the risk stratification of patients. In almost 50 percent of studies, some degree of patient risk stratification occurred.

Key findings

- Use of aspirin following major orthopedic surgery was generally found to be of similar effectivenessas other agents.
- An overwhelming majority of studiesconcluded that aspirin has a lower bleeding risk rate than other pharmacologic agents, which, combined with its lower cost, makes it an appealing option for VTE prophylaxis, particularly in low-risk patients.
- More prospective randomized controlled trials are needed to directly compare the effectiveness of aspirin with other prophylactic methods across patient risk levels.

Cross-cutting patient safety topics/practices

Over the last decade, there have been more quality and safety improvement efforts in healthcare than ever before, with programs funded by Federal grants, State agencies, and privately run organizations. Despite these efforts, reliably safe healthcare has remained somewhat elusive as adverse events continue to occur. A more recent trend in healthcare quality improvement has been focused on building high reliability organizations (HROs). HROs are described as organizations that operate in complex environments while maintaining high levels of safety for extended periods of time. HROs also have strong leaders who are committed to safety.

Leaders are key to instilling a commitment to safety in all members of the organization to create a positive safety culture, where staff continually scan and monitor their environment to identify and correct even minor deviations that could lead to unsafe conditions. When a deviation in safety processes or practices is observed, staff speak up or take action to contain the problem and/or resolve the issue. In the event that an adverse event or near miss does occur, incidents are reported without fear of blame or punishment. In addition, HROs rely on process improvement tools to systematically solve safety issues, including reliable assessments of the problem's scope (e.g., isolated to a unit or organization-wide), identification of root causes associated with the problem, and application of the most appropriate solutions.

While a great deal can be learned through the study of HROs, it can be difficult to articulate the exact steps to achieve high reliability, as many different paths can be taken. Moreover, what works in one organization does not always work in another, as demonstrated by the many conflicting results found within the healthcare quality and patient safety literature. To increase the reliability of healthcare quality, it is also necessary to understand the context in which improvement practices are applied. Any pre-existing norms, processes, resources, or quality improvement initiatives will influence how new practices are viewed and adopted, and the degree to which they achieve their intended result(s).

A wide range of contextual factors can impact performance. Four specific cross-cutting patient safety practices will be reviewed in this section: (1) patient and family engagement, (2) safety culture, (3) cultural competency, and (4) teamwork and team training.

Patient and family engagement

Traditionally, patient safety management has been the sole responsibility of the healthcare provider, but in recent decades, new approaches to patient safety include actively engaging patients and/or patients' families and caregivers. While there is no standard definition, patient and family engagement (PFE) is commonly defined as the desire and capability to actively choose to participate in care in a way that is uniquely appropriate to the individual, in cooperation with a healthcare provider or institution, for the purposes of maximizing outcomes or improving care experiences. This makes sense because patient-centeredness is a vital aspect of healthcare, and patients are uniquely positioned to provide information throughout an entire course of care.

Patient and family engagement can be conceptualized in two primary ways: (1) as an overarching principle that is applicable to many patient safety practices and (2) as a specific component of another particular patient safety practice.[130] Some strategies to encourage adoption of patient and family engagement patient safety practices include:

- Patient and family advisory councils, boards, and committees
- Team-based care
- Interventions to support medication safety
- Structured communication for patients, families, and primary care providers
- Teach-back
- Warm handoffs

As patient and family engagement is still an emerging patient safety practice there is little if any published research that provides comprehensive insight into its relationship to patient safety. Because such studies are limited, healthcare providers may find it difficult to apply appropriate guidelines and implement effective patient and family interventions in their current practice.

Patient safety in primary care continues to evolve, and so do the practices used to engage patients and families in their care. Strategies are needed to help patients and families understand the role of PFE in their safety. Healthcare providers also need to understand the importance of engaging patients in their care. In order to accomplish this, stakeholders should become more involved in the process to address the following: (1) building consensus on the definition and guidelines for implementing patient and family engagement, whether it is through an independent intervention or as part of another intervention within an existing PSP; (2) widening the research scope for patient and family engagement and patient safety; and (3) addressing priority areas for implementing patient and family engagement.

Safety culture

Many patient safety practices are available to reduce harms, but these practices sometimes fail to achieve their intended results. Even when implemented properly, contextual factors and organizational characteristics can reduce their effectiveness. For example, the patient safety culture can affect the degree to which patient safety practices are adhered to, or not. Patient safety culture, which is part of the overall culture, has been described as the beliefs, values, and norms that are shared by healthcare practitioners and other staff throughout the organization that influence their actions and behaviors. Patient safety culture helps inform staff about the behaviors that are acceptable, are worthy of praise, or are punishable (formally and/or informally) by the organization. A positive patient safety culture can be characterized as one where:

- Safety has been articulated as an organizational priority
- Staff work as a team to accomplish their tasks and reduce error
- There is open communication and transparency in discussing near-misses and adverse events
- There is an emphasis on learning from mistakes

Leaders in healthcare quality improvement have recognized the importance of safety culture and encouraged its measurement. Several safety culture survey instruments have been developed, and research has established their psychometric properties. For instance, AHRQ sponsored the development of Surveys on Patient Safety Culture™ (SOPS™) in multiple healthcare settings, such as hospital, medical office, nursing home, community pharmacy, and ambulatory surgery center. As part of this program, survey instruments and support materials are available, as are voluntary databases to which users can voluntarily submit data from patient safety culture surveys. These, as well as other safety culture surveys (e.g., Safety Attitudes Questionnaire) reliably measure multiple dimensions of safety culture, including teamwork, safety climate, communication, and error reporting.

Using such measures, studies have demonstrated a relationship between safety culture and a variety of patient outcomes. For instance, evidence suggests that perceptions of safety culture are related to readmission rates of cardiac patients, length of stay for intensive care unit patients, postoperative complication rates, medication errors, patients' perceptions of care, and safety incidents. Further, a positive safety culture may be a prerequisite for attaining safety goals, such that organizations with a favorable safety culture in place may be more likely to adopt new safety practices and have a better chance that those practices will take hold. As such, there is increasing interest in identifying the practices that lead to improved safety culture and evaluating their effectiveness.

BEFORE MOVING ONTO THE NEXT SECTION, PLEASE COMPLETE CASE STUDY 6.

Cultural competency

While there is not a single definition of cultural competency, a frequently cited definition, referenced by AHRQ, U.S. Department of Health and Human Services and others, comes from an early article by Cross et al. (1989),[132] who described the practice as, "A set of congruent behaviors, attitudes, and policies that come together in a system or agency or among professionals that enables effective interaction in a cross-cultural framework."

Historically, cultural competency consisted of teaching providers about different cultural groups. More recent pedagogy takes into account the dynamic nature of culture, in addition to intragroup variability, and social determinants of health such as socioeconomic status. Rather than categorizing and learning about different cultural groups, a more effective strategy is to teach providers skills that can be applied in any cross-cultural situation. Additionally, in recent years, there is greater focus on provider and organizational self-reflection, current and historical racism (and other forms of oppression), as well as structures of power and privilege, and how biases impact care.

While early understanding of cultural competency was limited to the provider/interpersonal level, the scope of cultural competency now includes the organizational and systems domains. For example, the U.S. Department of Health and Human Services established a framework for cultural and linguistic competency: The National Standards for Culturally and Linguistically Appropriate Services (CLAS) standards.[133] According to the CLAS standards, organizations that are culturally competent provide "effective, equitable, understandable, and respectful quality care and services that are responsive to diverse cultural health beliefs and practices, preferred languages, health literacy, and other communication needs."

Cultural competency is often framed as a best practice and as an achievable response to health and healthcare disparities in minority populations; it is also deemed an important practice in the context of increasing diversity in the U.S. population. The literature on cultural competency as a patient safety practice is limited; however, evidence suggests a link between provider and organizational cultural competency and patient safety.

Case Study 6: Leadership WalkRounds

Instructions: Spend 10 minutes reviewing the case below and considering the questions that follow.

Leadership WalkRounds are tools that executives and leaders can use to: increase awareness of safety; demonstrate their commitment to (and the importance of) safety; reinforce safety behaviors and concepts such as speaking up and non-punitive reporting; and gather and help solve patient safety– related issues.

As the term implies, this tool involves leaders "walking around" to engage in face to face, candid discussions with frontline staff about patient safety incidents or near-misses. Leadership WalkRounds vary in the way they are implemented, including the composition of the WalkRound team, the frequency with which WalkRounds are used, the degree of structure that each WalkRound follows (e.g., whether a standard set of questions is used), and the degree to which the WalkRound team communicates the issues raised and the potential solutions identified to the rest of the staff.

In 2002 the University of Michigan Medical Center instituted a version of WalkRounds in which the chief of staff met with caregivers every other week on individual patient care units.[131] Staff attendance was voluntary and confidential. The chief of staff opened meetings with the following statement:

"As you know, we're trying to move as an organization to more open communication and we're trying to develop a blame-free environment. We're doing this because we think this is the only and best way to make the environment safer for everyone who works here and for all of our patients. First, we're interested in focusing on our systems, not on individuals. In keeping with this, please know that everything you say is confidential and peer review protected. If you have any concerns, please let us know. As we discuss patient safety, please keep in mind the many areas to which these questions might apply, including medication errors, miscommunication between individuals, distractions, inefficiencies, protocol violations, and any others you can think of."

Over a span of four years 70 such meetings took place. In a comparison of staff who had participated in the WalkRounds and those who did not, staff who experienced the WalkRounds were more likely to report errors or near-misses and were more likely to perceive that their manager promotes patient safety and is non-punitive in response to staff errors. In addition, these staff members felt a greater sense of teamwork within their unit.

1. **Do you think this or some variation on a WalkRound would be feasible at your place of work? Why or why not?**

2. **What might be some potential barriers to implementing a WalkRound at your place of work?**

3. **How might patient safety be improved by instituting some kind of WalkRound at your place of work?**

As with many healthcare quality outcomes, studies have found disparities in adverse safety events between cultural and racial/ethnic groups in the United States. Safety outcomes in which certain groups experience disproportionately high adverse events include: healthcare-associated infections, diagnostic errors, adverse birth outcomes, medication errors (e.g., polypharmacy and adverse medication events), inappropriate care transitions; and failure to obtain patient directives. One study found that 49.1% percent of adverse events for Limited English Proficient (LEP) patients resulted in physical harm, whereas 29.5% of adverse events for patients who speak English resulted in harm.[134]

Patient–provider communication challenges and cross-cultural issues are at the root of many adverse events. Conversely, patients of physicians reporting greater cultural competency were more satisfied, and reported seeking and sharing more information during the medical visit. In one study, provider cultural competency was linked to higher prescribing of antiretroviral medications, patient medication adherence, and viral suppression in non-white HIV patients.[135] Tools specifically developed to mitigate potential adverse events, such as patient suicide, may be more effective when tailored to a patient's culture, and language services and language concordance between providers and patients have been associated with improved patient outcomes.

Implementation: challenges

Several barriers to implementing cultural competency practices have been identified, including translating training into practice and understanding the best methods for providing performance feedback to physicians. Another challenge is identifying patients' language needs.

A specific implementation issue is the underuse of professional interpreters in the clinical setting. This is despite the fact that language services are legally mandated and that providers have reported a preference for working with professional interpreters over ad hoc interpreters (family, friends, or untrained staff).

There are structural and provider-level reasons for underuse of interpreters, such as the fact that not all states provide reimbursement. For example, pediatricians in states with reimbursement had twice the odds of using a formal interpreter versus those in non-reimbursing states (odds ratio [OR] 2.34; 95% CI 1.24 to 4.40).[136] Barriers to interpreter use at the clinician level include lack of convenience and time pressures, as well as concerns about the quality of interpretation and resource constraints. While physicians have expressed a preference for in-person interpreters, use of telephone and video conferencing increases efficiency and may help to increase use of interpreters. To improve utilization, some have called for organizational resources and guidelines that are consistent with institutional policies and professional norms. Additionally, educational campaigns could help shift clinician culture away from ad hoc interpreters. Despite the cost of interpreter services, studies show that, ultimately, providing the service is cost-effective in terms of improved care. Sharing of resources across organizations has helped some facilities to overcome cost barriers. Finally, to address need, more effort could be made to recruit bilingual clinicians with appropriate training and certification.

Teamwork and team training

Failures in communication and teamwork have been identified as contributing factors in approximately 68% of adverse events.[11] Considerable effort has been made to improve teamwork within healthcare settings through the use of team training programs and performance support tools. Team-training is defined as a constellation of content (i.e., specific knowledge, skills, and attitudes (KSAs) that underlie targeted teamwork competencies, tools (i.e., team task analysis, performance measures), and delivery methods (i.e., information, demonstration and practice-based learning methods) that together form an instruction strategy.

Some of the earliest healthcare team training programs were based on Crew Resource Management (CRM), an established and validated strategy within the aviation community. Subsequently, the Veterans Health Administration introduced its own team training program, called Medical Team Training. Similarly, AHRQ partnered with the Department of Defense to develop a team training program specifically designed for healthcare providers called Team Strategies and Tools to Enhance Performance and Patient Safety (TeamSTEPPS). Introduced in 2006, TeamSTEPPS aims to improve a common set of team KSAs that providers can apply when working in any healthcare team.[137] Four specific, trainable skills are highlighted in the program: leadership, situation monitoring, mutual support, and communication.

Since its inception, TeamSTEPPS has become the national standard for team training in healthcare. In 2015, it was estimated that over 1.5 million individuals had been trained in TeamSTEPPS. One reason for this uptake is that TeamSTEPPS concepts are applicable across healthcare environments and the training (and associated support tools) are easily adaptable. Moreover, evaluation data collected on TeamSTEPPS and other team training programs have demonstrated positive results.

Team training programs such as TeamSTEPPS also include a variety of tools to help ensure that teamwork skills are transferred from the training environment and integrated into daily practices. Toward that end, performance support tools such as checklists, briefings, and huddles have been implemented to increase communication and teamwork in a variety of healthcare environments.

Crew resource management

CRM Training was originally developed to improve teamwork within the aviation community. CRM programs focus on improving attitudes toward and knowledge about teamwork, as well as increasing the use of teamwork skills. CRM programs generally follow a workshop format (i.e., classroom training) that includes a didactic lecture, demonstration of both positive and negative examples of teamwork, hands-on practice using teamwork skills (e.g., in role play exercises or simulation exercises), and feedback regarding the effectiveness of teamwork skills demonstrated by participants. A considerable amount of research on improving teamwork and communication within healthcare has applied CRM as an instructional strategy.

The systematic review of team training conducted by Weaver et al. (2014) included nine studies of CRM.[138] Four CRM studies in that review measured results through the collection of various clinical process and outcome measures. They reported that CRM was associated with improvements in clinical management scores, decreases in adverse outcome index (i.e., composite score of clinical outcomes), increases in standards in care (e.g., speed and completeness of resuscitations in the emergency department), and increased patient satisfaction.

Overall, results demonstrated positive results on process measures. Specifically, trainees reacted positively to the CRM training across studies, improved their knowledge of teamwork, and reported greater confidence in using teamwork skills. Importantly, data also indicated that trainees increased their use of team KSAs back on the job.

TeamSTEPPS® training

TeamSTEPPS is a team training program developed specifically for healthcare providers by the U.S. Department of Defense in collaboration with AHRQ. TeamSTEPPS training focuses on four trainable teamwork behaviors: communication, leadership, situation monitoring, and mutual support. The training imparts information on these behaviors, incorporates videos demonstrating positive and negative examples of the skills being used, and provides multiple tools that can be used to increase teamwork behaviors in healthcare settings. Although the TeamSTEPPS program has evolved over the years to include multiple settings (e.g., office-based care, long-term care), as well as online training modules, the studies in the current review followed the traditional TeamSTEPPS program for hospital settings.

MTT

In 2007, the Veterans Health Administration (VA) introduced its own team training program, MTT. MTT focuses on improving communication through a training workshop, as well as on the job through the implementation of team briefings before and after surgical cases. One study included in Weaver et al.'s (2014) systematic review found significant improvements in teamwork climate items reported for physicians and nurses.[138]

Team simulation

Simulation is another method used to improve teamwork skills. Simulation provides teams with realistic scenarios that they may face, either routinely or in emergencies. These scenarios allow participants to practice critical teamwork behaviors and receive feedback.

As noted in the review by Weaver et al. (2014), simulation is commonly used to train healthcare teams and can have high or low fidelity. High-fidelity simulations refer to those that strongly mimic real life scenarios, the actions that should be taken by the participant(s), and the actual work environment, including equipment and patients. Low-fidelity simulations present realistic scenarios and require participants to react as they would in the real world but do not replicate all aspects of the environment (e.g., a doll could be used in place of a mannequin).

Briefings

Briefings have a long history of use in the field of aviation and have been included as a tool within healthcare CRM programs, as well as in the TeamSTEPPS training program. Prebriefings help set the stage for teamwork by reviewing tasks that need to be accomplished, identifying which team member(s) will be responsible for each task, and discussing any contingency plans. Debriefings then review (post- performance) what went well and what could have gone better, with the goal of improving performance in the future. Debriefings can cover a combination of individual and team performance as well as system issues.

Handoff protocol

Handoff protocol is a tool that can be used to increase teamwork during patient transitions. Such transitions occur between shifts within a unit or when a patient is transferred from one unit to another (e.g., from the OR to the surgical ICU). During this time, critical information needs to be passed that, if missed, can affect the quality of care. A standardized handoff protocol can ensure that information is consistently exchanged between providers.

Checklists

Checklists constitute another tool that has historically been used in the aviation industry, specifically during the pre-flight phase. Checklists are well suited for completing procedural tasks and have been implemented as a way to improve teamwork (especially to increase communication among team members) and to reduce technical errors.

Conclusions

In terms of team training programs, training was most often delivered in a 4- to 5-hour session and evaluated within a specific unit (e.g., obstetrics, ICU), although some studies conducted training at the hospital level. Improvements were demonstrated on a variety of process measures (indicative of reaction, learning, and transfer criteria) and outcome measures (i.e., results criteria) relevant to the participants' settings.

Tools such as checklists and briefings may appear to require less time or fewer resources to implement than team training programs such as those described. However, time and due diligence are needed to educate staff on why the selected tool is being implemented, how to use the tool, and how the tool fits into the established workflow. Once implemented, new protocols sometimes required greater time and participation by the entire team to ensure all elements were covered.

Leadership involvement and project champions are key regardless of the specific practice used to improve teamwork. Leadership support is needed not only to help get a practice off the ground, but also to ensure compliance over time. For example, leaders may be involved in promoting or endorsing the training, as well as participating in (or being present during) team training workshops. In the case of implementing performance support tools on the job, leadership support can signal that the improvement tools are critical to quality and safety of care rather than merely an additional administrative task.

Additionally, leadership can provide reinforcement when staff use the tools as intended and help ensure that their use is sustained over time. As mentioned earlier, researchers suggest that studies that assess multiple criteria, measure KSAs at multiple levels, and/or incorporate multiple measurement methods provide the most meaningful evaluation data regarding an intervention's effectiveness.

Collectively, research supports the use of team training interventions and performance support tools for improving teamwork, sustaining those improvements on the job, and positively influencing clinical and patient outcomes.

Learning activity Summary

This activity covers a range of patient safety practices chosen for the high-impact harms they address and interest in the status of their use. The harms include diagnostic errors, failure to rescue, sepsis, infections due to multi-drug resistant organisms, adverse drug events, and nursing-sensitive conditions.

The most significant harms patients face continue to be found in higher acuity settings, such as the emergency department and intensive care units. Research on the use of sepsis screening tools, for example, predominantly takes place in the acute care setting. As the importance of early identification has gained traction, sepsis screening tools are now being investigated for use in pre-hospital and long-term care settings, although with widely varied results.

Other harms, such as adverse drug events and diagnostic errors, occur in a variety of settings. For example, reducing adverse drug events in the elderly using medication deprescribing practices or medication screening, as well as associated research, can be found in ambulatory settings, long-term care facilities, and acute care settings. Similarly, PSPs geared toward reducing diagnostic errors, such as the use of clinical decision support in the diagnostic process, peer review of radiology and pathology studies, or result notification systems, have been studied in both the ambulatory and acute care settings.

One aspect of care or "setting" that poses a unique threat to patients is the transition between one setting and another; from the hospital to the outpatient setting, in particular. Two address harms associated with transitions of care: care transition models as a PSP to reduce readmissions and medication management across transitions to reduce adverse drug events.

Regardless of setting, several themes have been repeatedly stressed in this activity:

- More than one PSP can be used to reduce a given harm.
- Selecting a particular PSP for implementation in a specific healthcare facility or system should be based on the predominant root cause(s) of the harm at that facility or system. For example, in one facility, theroot cause of an increase in sepsis mortality may be a lack of recognition of patients with sepsis arriving to the emergency department. In another facility, it may be due to lack of monitoring of patients who are experiencing deterioration on a medical-surgical unit.
- When using a specific PSP, consideration must be given to potential new harms that can be introduced. For example, PSPs and strategies to reduce venous thromboembolism must take intoaccount the potential to unintentionally increase anticoagulation-related events.
- PSPs are not implemented in isolation and are often part of a broader safety strategy. The strategy often relies on a strong safety culture, teamwork, communication, and involvement of the patient and family. These cross-cutting practices are the foundation for success.

It is clear that when it comes to improving patient safety, the importance of context for implementation cannot be overstated. Setting, safety culture, staffing and other organizational factors contribute to harm reduction as much as a PSP itself. We often know what to do. Now the challenge is how to implement effective PSPs into specific facilities or settings and have them succeed.

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Self-Assessment

Choose the best possible answer for each question and mark your answers on the self-assessment answer sheet at the end of this book. There is a required score of 70% or better to receive a certificate of completion.

21. What percentage of adults are reported to be affected by diagnostic errors in the outpatient environment?

A. 1.5%.
B. 3%.
C. 5%.
D. 8%.

22. A useful framework for achieving success in clinical decision support design, development, and implementation is the _____ approach.

A. Health IT paradigm.
B. CDS Five Rights.
C. Medical Digital Interface.
D. Electronic Systems Integration.

23. Which phase of the general medical testing process is a known source of diagnostic errors?

A. Pre-analytic.
B. Inter-analytic.
C. Analytic.
D. Post-analytic.

24. What is a potential safety concern related to Clinical Decision Support (CDS) software?

A. May override clinician decisions.
B. Alert fatigue generated by high rates of computer-generated alerts.
C. Prescription of non-preferred medications.
D. May raise risk of medication errors.

25. Which teaching tool has been found to be associated with large positive effects on improving clinical reasoning skills among clinicians?

A. The use of virtual patients in training.
B. Feedback training.
C. Grand rounds.
D. Case study review.

26. What term describes an alarm system that works as designed but signifies an event that is not clinically significant?

A. Monitoring device alarm.
B. False positive alarm.
C. False negative alarm.
D. Non-actionable alarm.

27. Studies have shown that the percentage of false alarms in healthcare settings can range from ___ to ___?

A. 42% to 69%.
B. 52% to 79%.
C. 62% to 89%.
D. 72% to 99%.

28. Which of the following is a strategy for reducing the risk that medical staff will experience alarm fatigue?

A. Raising the thresholds at which monitoring systems produce an alarm.
B. Eliminating alerts embedded in EHR systems.
C. Fostering a safety culture in the organization.
D. Designating one staff member on each shift to be the one who receives alerts, rather than the entire staff.

29. What have many national organizations suggested as an important step in alarm management?

A. Conducting a baseline alarm assessment.
B. Training nurses to turn off unnecessary alarm systems.
C. Engaging organizational leadership in decisions about reducing alarm fatigue.
D. Updating clinical status monitors with devices that have lower sensitivities for physiological variables in order to reduce the incidence of false alarms.

30. What is the rate of death among people aged 65 and older from healthcare-associated *C. difficile* infection?

A. 1 in 11.
B. 1 in 15.
C. 1 in 20.
D. 1 in 22.

31. Approximately how many people die from *C. difficile* infections every year in the U.S.?

A. 25,000.
B. 30,000.
C. 35,000.
D. 40,000.

32. What is the name of the general approach to reducing the use of antibiotics and reducing the evolution of antibiotic-resistant bacteria?

A. Antimicrobial accountability and education programs.
B. Antibiotic harm reduction.
C. Antimicrobial stewardship.
D. Antibiotic mitigation programs.

33. Which class of antibiotics do guidelines specifically target for reduced or restricted use as one a way to reduce *C. difficile* infections?

A. Tetracyclines.
B. Aminoglycosides.
C. Cephalosporins.
D. Macrolides.

34. In the past decade, what practice has received increasing attention as a potential way to reduce a major source of *C. difficile* transmission in healthcare settings?

A. Patient hand hygiene.
B. Medical device decontamination.
C. Clinician hand hygiene.
D. Use of telemedicine.

35. Which cleaning agents for washing surfaces by hand demonstrate the best evidence for killing *C. difficile*?

A. Chlorine-releasing solutions.
B. Antimicrobial detergents.
C. Alcohol-based disinfectants.
D. Hydrogen peroxide.

36. Which two factors are considered to pose the greatest risk of drug-related adverse events among adults age 65 years and older?

A. Polypharmacy and the use of potentially inappropriate medicines.
B. Inappropriate use of antibiotics and over-use of corticosteroids.
C. Inappropriate dosing adjustments for older age and over-use of antibiotics.
D. Patient use of un-regulated supplements and over-use of acetaminophen.

37. What is the name of efforts to reduce the potential harms to older adults posed by polypharmacy?

A. Geriatric prescribing practices.
B. Clinically appropriate prescribing.
C. Rational prescribing.
D. Deprescribing.

38. Which kind of intervention related to prescriptions has been shown to decrease hospitalizations and ED visits in older adults?

A. Clinical decision-support systems.
B. Pharmacist-led medication review.
C. Patient education about polypharmacy.
D. Automated prescription refill reminders.

39. Which protocol/criteria has been shown to reduce adverse drug events among older adults?

A. STOPP.
B. BOOST.
C. CTI.
D. TCM.

40. What is a notable barrier to implementing deprescribing protocols for older adults?

A. Pharmacists not adhering to implementation protocols.
B. Inadequate documentation of medication history.
C. Patients being discouraged from discontinuing medications by their provider.
D. All of the above.

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Final exam questions are located at the end of each chapter.

Best Practices for Treating Pain with Opioid Analgesics

	A	B	C	D
1	○	○	○	○
2	○	○	○	○
3	○	○	○	○
4	○	○	○	○
5	○	○	○	○
6	○	○	○	○
7	○	○	○	○
8	○	○	○	○
9	○	○	○	○
10	○	○	○	○

Evidence-Based Guidance on Prescribing Controlled Substances

	A	B	C	D
11	○	○	○	○
12	○	○	○	○
13	○	○	○	○
14	○	○	○	○
15	○	○	○	○
16	○	○	○	○
17	○	○	○	○
18	○	○	○	○
19	○	○	○	○
20	○	○	○	○

Existing and Emerging Patient Safety Practices

	A	B	C	D		A	B	C	D
21	○	○	○	○	31	○	○	○	○
22	○	○	○	○	32	○	○	○	○
23	○	○	○	○	33	○	○	○	○
24	○	○	○	○	34	○	○	○	○
25	○	○	○	○	35	○	○	○	○
26	○	○	○	○	36	○	○	○	○
27	○	○	○	○	37	○	○	○	○
28	○	○	○	○	38	○	○	○	○
29	○	○	○	○	39	○	○	○	○
30	○	○	○	○	40	○	○	○	○

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LEARNER RECORDS: EVALUATION

You must complete the program evaluation and applicable activity evaluation(s) in order to earn *AMA PRA Category 1 Credits*™, MOC points, or participation in MIPS. For each of the objectives determine if the activity increased your:

A Competence B Performance C Outcome D No Change

COURSE 1 - BEST PRACTICES FOR TREATING PAIN WITH OPIOID ANALGESICS:

		A	B	C	D
1.	Identify and employ a full range of therapeutic options when developing a pain treatment plan..	○	○	○	○
2.	Screen patients for presence or risk of OUD, assess and manage patients who demonstrate signs of OUD, or refer if necessary. .	○	○	○	○

3. Please identify a specific change, if any, you will make in your practice related to safe prescribing of opioid analgesics._____

4. What do you see as a barrier to making these changes?_____

COURSE 2 - EVIDENCE-BASED GUIDANCE ON PRESCRIBING CONTROLLED SUBSTANCES:

		A	B	C	D
5.	Develop optimal treatment regimens when using controlled substances for common medical conditions through patient evaluation, and track potential misuse through recommended usage of monitoring measures.	○	○	○	○
6.	Comply with federal, state, and local regulations regarding prescribing of controlled substances and utilize strategies for diagnoses and treatment of OUD	○	○	○	○

7. Please identify a specific change, if any, you will make in your practice related to safe prescribing of controlled substances._____

8. What do you see as a barrier to making these changes?_____

COURSE 3 - EXISTING AND EMERGING PATIENT SAFETY PRACTICES:

		A	B	C	D
9.	Protect patient safety by understanding system-level or organization-level factors involved with medical errors or harms.	○	○	○	○
10.	Improve system-level or organization-level factors to further reduce medical errors or harms.	○	○	○	○
11.	Identify patient-centered strategies that can help reduce potential harms	○	○	○	○
12.	Implement patient-centered strategies to help reduce rates of hospital-acquired infections and a range of other potential harms, such as adverse events	○	○	○	○

13. Please identify a specific change, if any, you will make in your practice related to improving patient safety._____

14. What do you see as a barrier to making these changes?_____

OVERALL PROGRAM:

		Yes	No	If no, please explain:
15.	The program was balanced, objective & scientifically valid	○	○	_____
16.	Do you feel the program was scientifically sound & free of commercial bias or influence? .	○	○	_____

17 How can this program be improved?_____

18. Based on your educational needs, please provide us with suggestions for future program topics & formats. _____

19. For which activities would you like to use your participation as a clinical practice improvement activity (CPIA) for MIPS?

○ Course 1 ○ Course 2 ○ Course 3 ○ None

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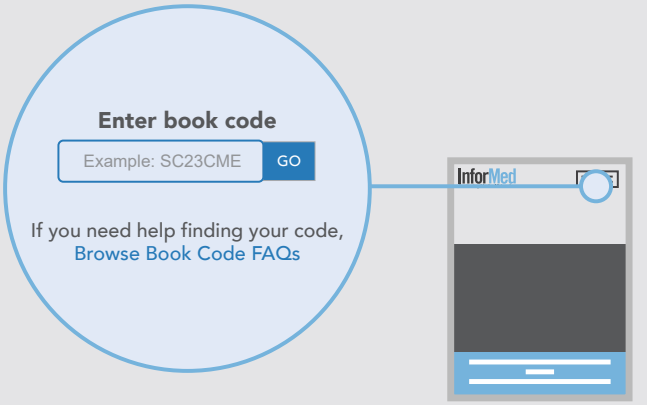

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