InforMed
Continuing Medical Education
By Colibri Healthcare

State Specific Continuing Medical Education

2023 Kentucky Medical Licensure Program

- **4.5 HOURS**
  HB 1 / Pain Management / Addiction / KASPER*

Current Three-Year CME Cycle:
January 1, 2021 - December 31, 2023

ACCME ACCREDITED

*Physician CME Requirement:

Four and one-half (4.5) credits relating to the use of KASPER, pain management, addiction disorders or a combination of two or more in these content areas.

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

KYPHY.CME.EDU

CONTENTS

2023 KENTUCKY

*Complete courses 1 & 2 to fulfill mandatory 4.5 credits of HB 1 CME.

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.

$75.00
ENTIRE PROGRAM

$55.00
COURSES 1 & 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, e-mail 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

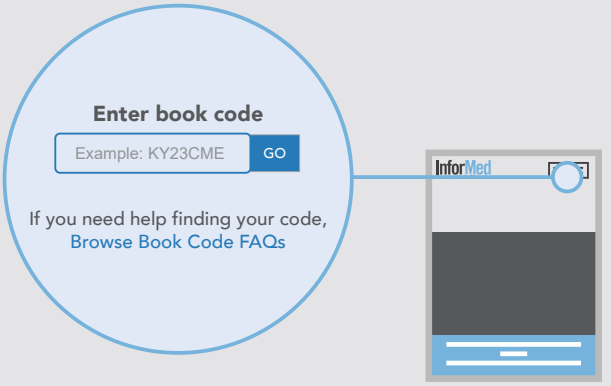
Please read these instructions before proceeding.

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.

Fastest way to receive your certificate of completion

Online

- Go to **BOOK.CME.EDU**. Locate the book code **KY23CME** 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	Credits	Code	Price
Entire Program	17	KY23CME	$75.00
Courses 1 & 2	5	KY23CME-55	$55.00

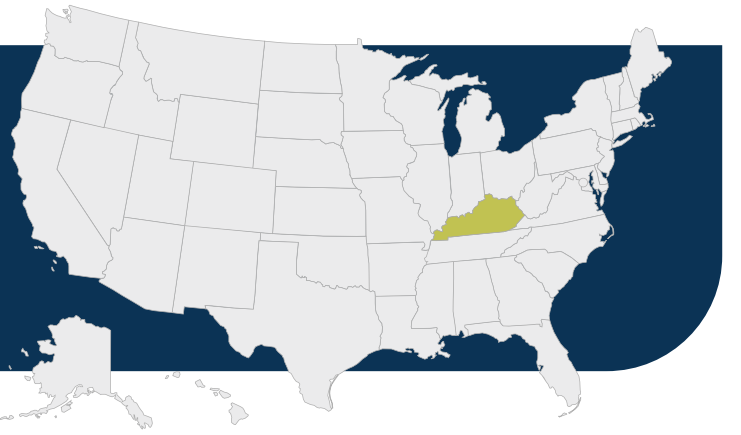
By mail

- 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 e-mail 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.

INFORMED TRACKS
WHAT YOU NEED, WHEN YOU NEED IT



Kentucky Professional License Requirements

PHYSICIANS CONTINUING MEDICAL EDUCATION REQUIREMENTS FOR LICENSE RENEWAL

The Kentucky Board of Medical Licensure requires all physicians maintaining a current license to complete sixty (60) credits of continuing medical education during the three (3) year CME cycle, of which at least thirty (30) credits shall be *AMA PRA Category 1 Credits*™. The current CME cycle started January 1, 2021 and ends December 31, 2023.

MANDATORY CONTINUING MEDICAL EDUCATION REQUIREMENTS

KASPER, PAIN MANAGEMENT AND ADDICTION DISORDERS

The Kentucky Board of Medical Licensure requires that the number of credits of continuing medical education must include four and one-half (4.5) credits relating to the use of KASPER, pain management, addiction disorders or a combination of two or more these content areas. Licensees who have a valid DEA registration, can dispense or prescribe controlled substances, and are not exempted must complete this requirement during each CME cycle.

What This Means For You:

For the CME cycle ending December 31, 2023 physicians must complete 60 continuing medical education credits, of which at least 30 shall be A*MA PRA Category 1 Credits*™. For physicians who prescribe or dispense controlled substances in Kentucky, the 30 credits of Category 1 must include 4.5 credits relating to the use of KASPER, pain management, addiction disorders or a combination of two or more in these content areas. For information on Kentucky CME requirements go to http://kbml.ky.gov/cme/Pages/default.aspx.

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

Kentucky Board of Medical Licensure
310 Whittington Pkwy #1B
Louisville, KY 40222
P: (502) 429-7150
F: (502) 429-7158

CME RENEWAL CYCLE:
1/1/2021 to 12/31/2023

LICENSE TYPES:
MD/DO

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**
Effective Management of Acute and Chronic Pain with Opioid Analgesics	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
Alternatives to Opioids for Treating Pain	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
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.

EFFECTIVE MANAGEMENT OF ACUTE AND CHRONIC PAIN WITH OPIOID ANALGESICS

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 other health care professionals involved 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

This CME learning activity is designed to increase physician knowledge and skills about guideline-recommended principles of pain management, the range of opioid and non-opioid analgesic treatment options, and specific strategies for minimizing opioid analgesic prescription, diversion, and abuse.

LEARNING OBJECTIVES

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

1. Identify the range of therapeutic options for managing acute and chronic pain, including non-pharmacologic approaches and pharmacologic therapies.
2. Explain how to integrate opioid analgesics into a function-based pain treatment plan individualized to the needs of the patient, including counseling patients and caregivers about the safe use of opioid analgesics.
3. Discuss recommendations and rationale for incorporating emergency opioid antagonists into prescribing practice for training patients and family members on the use of naloxone.
4. Identify medications currently approved for the treatment of opioid use disorder and the ways these medications differ in terms of mechanisms of action, regulatory requirements, and modes of administration.

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.

FACULTY

Paul J. Christo, MD, MBA
Associate Professor, The Johns Hopkins University School of Medicine
Director, Multidisciplinary Pain Fellowship Program (2003-2011)
Director, Blaustein Pain Treatment Center (2003-2008)
Division of Pain Medicine

Annette Skopura, PHD
Medical Writer
EnlightenMed

ACTIVITY PLANNER

Michael Brooks
CME Director
InforMed

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

3

Pain Management and Addiction Disorders

KENTUCKY SPECIAL APPROVAL:

This course satisfies three (3) CME credit hours in pain management and addiction disorders.

The Kentucky Board of Medical Licensure requires physicians who prescribe or dispense controlled substances in Kentucky to complete four and one-half (4.5) hours of CME relating to the use of KASPER, pain management, addiction disorders, or a combination of two or more of those subjects.

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:

- Annette Skopura, PHD
- Michael Brooks

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

- Paul J. Christo, MD, MBA has received honoraria from GlaxoSmithKline and Eli Lilly.

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 pain management

Physicians caring for patients in pain face an unusually daunting set of challenges. As with many other chronic conditions, clinicians must carefully balance expected benefits of treatment with the potential for harm from such treatments. Treating pain, however, involves an additional level of complexity because one of the most commonly-used classes of pain medications—opioids—are at the center of national efforts to stem the epidemic of opioid-related abuse, addiction, and overdose.[1]

The United States has seen three successive waves of opioid overdose deaths related to both legal and illegal opioids (Figure 1).[2] 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).[3] 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.[4] The surge was primarily driven by a 34% increase in overdose deaths related to synthetic opioids, primarily fentanyl.[4] Overdose rates appear to have accelerated during the COVID-19 pandemic.[5] Between 1999 and 2019, the CDC estimates that nearly 500,000 people in the United States died from such overdoses.[6]

Coupled with rising rates of overdose death are equally dramatic increases in the number of people misusing or abusing opioids. As many as 1 in 4 patients on long-term opioid therapy in a primary care setting are estimated to be struggling with opioid use disorder (OUD), also called opioid addiction.[7-9] In 2016 approximately 11.5 million Americans reported misusing prescription opioids in the previous year.[10] According to the federal Substance Abuse and Mental Health Services Administration (SAMSHA), approximately 80% of heroin users started on their path to addiction after using oral opioid analgesics (either prescribed to them or illicitly).[11]

Although the rates of opioid prescriptions have leveled off or declined slightly in recent years, the average days of supply per opioid prescription has continued to rise [10]

It is against this background that providers must make daily decisions about how best to treat their patients in pain. Unfortunately, many providers are unfamiliar with the growing evidence base suggesting that opioids are actually not very effective for relieving chronic non-cancer pain in the long-term and, in fact, may be associated with harms such as increased pain, reduced functioning, and physical opioid dependence.[12,13] Providers may also not be aware of the expanding range of both non-opioid medications and non-pharmacological therapies shown to be effective in reducing many common chronic pain conditions.

This CME learning activity discusses the management of chronic and acute pain in a variety of patient populations and is structured to conform to the latest Food and Drug Administration (FDA) Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain (2018). It reviews evidence for non-opioid therapies, including non-drug and non-opioid drug options, as well as current evidence regarding opioid efficacy, harms, and overdose prevention with naloxone, and how to slowly and safely taper opioid doses.

Key opioid-related terms

Opioid: any psychoactive chemical resembling morphine, including opiates, and binding to opioid receptors in the brain. This term describes opioid and opiates.

Opiate: "natural" opioids derived from the opium poppy (e.g., opium, morphine, heroin).

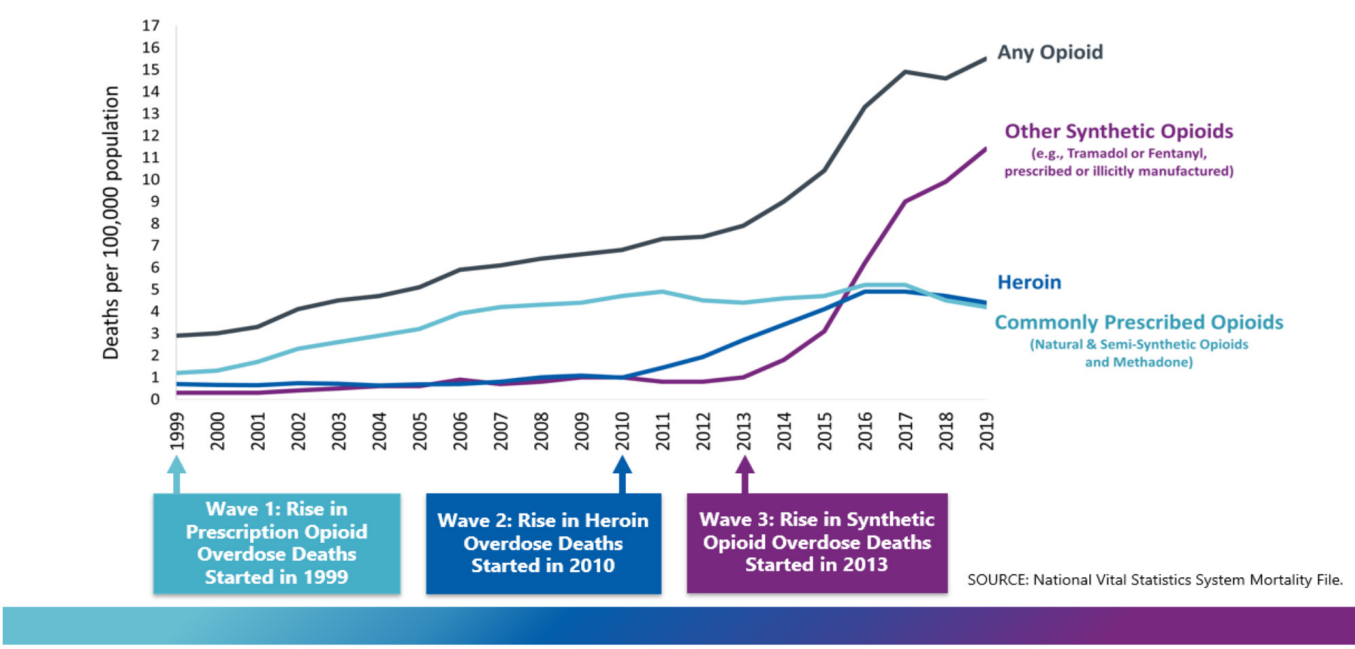
Semi-synthetic opioids: analgesics containing both natural and manufactured compounds (e.g., oxycodone, hydrocodone, hydromorphone, oxymorphone).

Synthetic opioids: fully-human-made compounds (e.g., methadone, tramadol, and fentanyl).

Types of Pain

Differentiating between nociceptive and neuropathic pain is critical because the two respond differently to pain treatments. Neuropathic pain, for example, may respond poorly to both opioid analgesics and non-steroidal anti-inflammatory (NSAID) agents.[14] Other classes of medications, such as anti-epileptics, antidepressants, or local anesthetics, may provide more effective relief for neuropathic pain.[15]

Figure 1. Opioid-related overdose deaths by type in the United States[6]



Another important dimension of pain is its effects beyond strictly physiological functioning. Pain is currently viewed as a multi-dimensional, multi-level process similar in many ways to other disease processes which may start with a specific injury but which can lead to a cascade of events that can include physical deconditioning, psychological and emotional burdens, and dysfunctional behavior patterns that affect not just the sufferer, but their entire social milieu (illustrated in Figure 2).[16]

Although pain is expected after injury or surgery, the patient pain experience can vary markedly. The intensity of pain can be influenced by psychological distress (e.g., depression or anxiety), heightened illness concern, or ineffective coping strategies regarding the ability to control pain and function despite it.[17] It may also be shaped by personality, culture, attitudes, and beliefs.

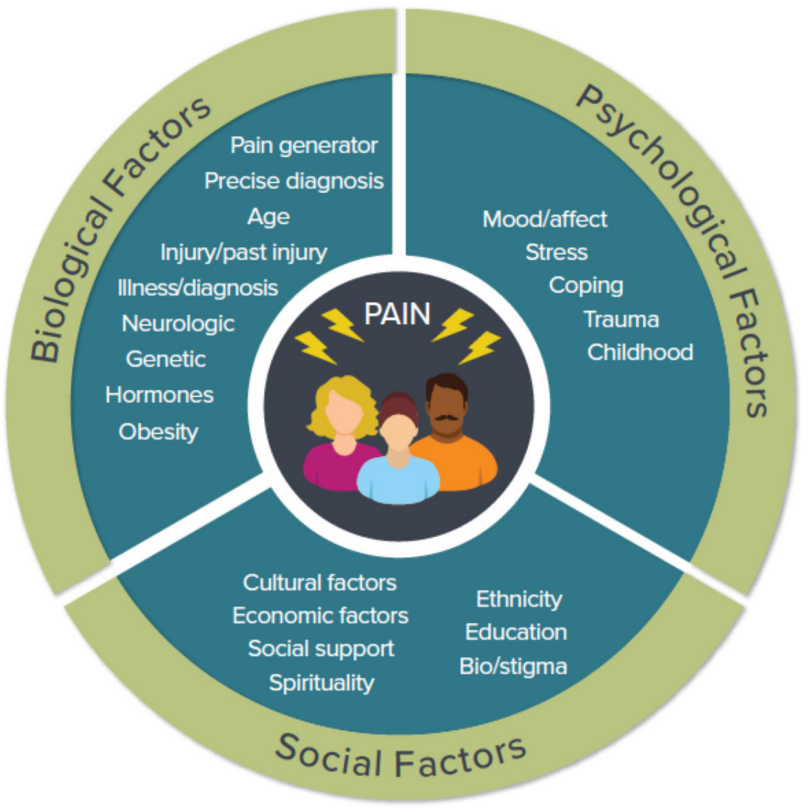
Evaluating pain

Take a history

The patient's self-report is the most reliable indicator of pain.[18] Physiological and behavioral signs of pain (e.g., tachycardia, grimacing) are neither sensitive nor specific for pain and should not replace patient self-report unless the patient is unable to communicate. Therefore, talking to patients and asking them about their pain (i.e., obtaining a "pain history") is integral to pain assessment.

The pain history usually is obtained as part of the patient history, which includes the patient's past medical history, medications, habits (e.g., smoking, alcohol intake), family history, and psychosocial history. Obtaining a comprehensive history provides many potential benefits, including improved management, fewer treatment side effects, improved function and quality of life, and better use of health care resources.

Figure 2. The Biopsychosocial Model of Pain[16]



Assessing the impact of pain on functional status and sleep and screening for mental health conditions potentially related to pain or treatment adherence (e.g., depression, anxiety, and memory issues) may provide useful information for pain management.[19] Depression in older patients, for example, sometimes presents with somatic complaints of pain. Pain complaints may resolve when the underlying depression is treated. Patients can also be screened for known risk factors for OUD (see below).

Tools

Many tools have been developed to document and assess pain. Initial approaches to assessing pain severity use a numerical rating scale (NRS) rating pain from 0 (no pain) to 10 (worst pain you can imagine) (some scales use a 0 to 100 scale). Such scales are often used in clinical trials of pain therapies, and the minimal clinically important difference using these scales is generally considered a 20%-30% change from baseline (i.e., 2-3 points on a 0-10 scale or 20-30 points on a 0-100 scale).[20]

Multidimensional tools, such as those described below, include questions relating to quality of life and participation in daily activities. Such tools can provide a more comprehensive approach to assessing pain and response to treatment. The selection of a pain assessment tool must balance the comprehensiveness of the assessment obtained with the time and energy required to use the tool in a real-world practice setting.

Brief pain inventory

The Brief Pain Inventory (BPI) is used frequently in clinical trials to assess pain. Specifically developed for patients with chronic pain, the BPI more fully captures the impact of pain on patient function and quality of life than simple VAS scales.[21] By including a pain map, the BPI allows tracking of the location of pain through the course of management. The BPI is self-administered but somewhat time-consuming, which may limit its role in a busy clinical practice.

PEG scale

The PEG scale (Pain average, interference with Enjoyment of life, and interference with General activity) is a three-item tool based on the BPI and is practical for clinical practice (Figure 3).

Figure 3: PEG scale[22]

What number best describes your pain on average in the past week?

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

Zero-to-10 scales are used to assess pain, enjoyment of life, and general activity. PEG can be self-administered or done by the clinician and is relatively brief. [22]

Assessing acute pain

Acute pain intensity can be assessed with unidimensional tools such as the VAS and the Wong-Baker FACES Pain Rating Scale (faces depicting increasing levels of pain). While useful for a quick assessment, these scales alone may not appropriately identify patients with pain-related suffering driven by functional limitations, worry, or other factors, and may not detect some patients with clinically significant pain.[23]

Although developed for patients with chronic pain, the BPI is also applicable to patients with acute pain. Completed by the patient, the BPI captures ways that pain impacts function and quality of life, although, like most multidimensional questionnaires, it requires more time (about 10 minutes) and concentration to complete, which may limit its utility in some elderly patients.[21]

Pain in patients with dementia

Although patients with mild-to-moderate dementia can report their pain and its location, those with severe dementia are often unable to communicate their pain experience or request medication. In these patients, physicians need to observe pain behaviors, including facial expressions, verbal cues, body movements, changes in interpersonal interactions, activity patterns, and mental status. Caregiver observations and reports are critical to appropriate assessment and management of chronic pain conditions.[24]

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

Chronic pain that develops after acute pain

A number of factors have been associated with an increased risk for chronic pain following acute pain or surgery including older age, psychological problems, higher levels of pre-procedural pain or pain sensitivity, type and duration of surgery, severity and number of comorbidities, and use of post-procedural radiation or chemotherapy.[25]

Some tools have been developed to help clinicians predict the likelihood that a patient will experience chronic pain following acute injury or procedures. The 5-item PICKUP model, for example, showed moderate prognostic performance in a derivation study using data from 2,758 patients with acute low back pain.[26] And Sipila and colleagues developed a 6-item screening instrument for risk factors of persistent pain after breast cancer surgery based on a cohort of 489 women.[27]

Case Study 1

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

Maurianne is an 85-year-old woman living in a residence facility for people with Alzheimer disease. Her cognition has deteriorated slowly in the seven years she has lived at the facility and now her speech is often a rambling, incoherent stream-of-consciousness, that she only seldom recognizes as such. Maurianne fell and sustained a right femur fracture requiring internal fixation. On the second day after surgery, the hospital nurse noted that Maurianne had an order for acetaminophen every 6 hours as needed. Although Maurianne was lying still and did not appear to be in distress, the nurse contacted the nursing home nurse who reported that Maurianne rarely lies still. The nursing home nurse explained that they assess pain using the Pain Assessment in Advanced Dementia (PAINAD) tool and emailed a copy to the hospital nurse. A review of the medical chart indicated that Maurianne slept intermittently the previous night, and when she conducted a physical examination, Maurianne seemed rigid and exhibited shallow breathing at a rate of about 20 breaths per minute. The nurse used the PAINAD behavioral tool to assess Maurianne's pain and the result suggested a positive score for possible pain. The nurse immediately called the surgeon and received an order for 1-2 mg morphine every 8 hours over the next 3 days. After the first dose, Maurianne's body relaxed, and her breathing became regular at a rate of 14 per minute. Later that evening, Maurianne slept 7 hours.

1. **Do you think the initial script for acetaminophen was appropriate for this patient? If now, what would you have prescribed?**

2. **How might Maurianne's cognitive impairments affect her pain management plan?**

3. **What other tools or techniques might be used to characterize Maurianne's level of pain or her response to prescribed analgesics?**

Screen for opioid abuse risk factors

Screening and monitoring in pain management seeks to identify patients at risk of substance misuse and overdose as well as improve overall patient care. Evaluations of patient physical and psychological history can screen for risk factors and help characterize pain to inform treatment decisions. Screening approaches include efforts to assess for concurrent substance use and mental health disorders that may place patients at higher risk for OUD and overdose. This includes screening for drug and alcohol use and the use of urine drug testing, when clinically indicated. These approaches enable providers to identify high-risk patients so that they can consider whether to prescribe opioids, engage substance misuse and mental health interventions, and education materials to mitigate opioid misuse.[16]

Many tools have been developed for the formal assessment of a patient's risk of having a substance misuse problem, some of which are appropriate for routine clinical use because they are relatively brief and easily implemented. Table 1 lists the tools that appear to have good content and construct validity for assessing patient risks related to chronic opioid therapy, although to date, no single tool has been widely endorsed or thoroughly validated.[28]

The Screening, Brief Intervention and Referral to Treatment (SBIRT) is an evidence-based tool used to facilitate screening patients for OUD, which typically takes 5-10 minutes to administer.[29] SBIRT has been endorsed by the Substance Abuse and Mental Health Services Administration (SAMHSA), but should always be paired with referral to treatment.[30] SAMHSA recommends universal screening with oral or writing-based tools because of the high prevalence of substance use disorders in patients visiting primary care settings. In contrast, universal screening with urine, blood, or oral fluid tests are not recommended.[30] In the context of pain care, however, the 2016 CDC guidelines recommend urine drug testing before initiating opioid therapy and probably at least annually when prescribing opioids for chronic pain.[31]

Other tools for universal substance abuse screening include:

- Single screening question screening tool for drug use
- Drug Abuse Screening Test (DAST) 10
- Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST)
- Tobacco, Alcohol, Prescription medication, and other Substance use (TAPS)
- the CAGE questionnaire adapted to include drugs (CAGE-AID)

Use drug monitoring programs

As of March, 2020, all U.S. states (except Missouri) and the District of Columbia have operational prescription drug monitoring programs (PDMPs).[32,33] Information available through PDMPs varies based on reporting requirements and restrictions, but may include DEA schedules reported, timeliness of pharmacy dispensing information, access, and required reviews.

Recommendations for using a PDMP include:

- Check the PDMP before starting anyone on opioid therapy.
- Review the PDMP periodically throughout opioid therapy (at least every 3 months).
- Look for prescriptions for other controlled substances, like benzodiazepines, that can increase risk of overdose death.
- Review the total MMED (Morphine Milligram Equivalent Dose).

Some states have specific requirements for PDMP use, such as requiring review prior to initial prescription or any time a specific prescription is written, such as for hydrocodone ER (Zohydro), therefore clinicians should remain updated about the specific requirements of their state PDMPs.

Urine drug testing

Urine drug testing (UDT) is recommended before prescribing any opioid and at least annually thereafter.[31] Providers using urine drug screens should be familiar with the metabolites and expected positive results based on the opioid prescribed. For example, a patient taking oxycodone may test positive for both oxycodone and oxymorphone (a metabolite).[34]

UDT often involves both presumptive (screen) testing, and definitive (quantitative) testing because many synthetic and semisynthetic opioids cannot be detected by presumptive testing alone.[35,36]

If the prescribed opioid is not detected, discuss the finding with the patient and, if diversion is confirmed or suspected, re-evaluate the pain management strategy or taper the opioid. If the patient tests positive for unprescribed drugs, schedule more frequent follow-up visits, consider opioid discontinuation, offer naloxone, or refer for treatment for substance use disorder. Decision tools and help with interpreting urine drug testing results are available at: http://mytopcare.org/udt-calculator/interpret-opiates-test-result.

Pain management overview

Many pharmacologic and non-pharmacologic approaches to treating pain are available to primary care providers.

These options should be employed using the following general principles:

- Identify and treat the source of the pain, if possible, although pain treatment can begin before the source of the pain is determined
- Select the simplest approach to pain management first. This generally means using non-pharmacologic approaches as much as possible and/or trying medications with the least severe potential side effects, and at the lowest effective doses
- Establish a function-based, individualized treatment plan if therapy is expected to be long-term

Non-drug approaches

Many nonpharmacologic and self-management treatment options have been found to be effective alone or as part of a comprehensive pain management plan, particularly for musculoskeletal pain and chronic pain.[37] Examples include, but are not limited to, psychological, physical rehabilitative and surgical approaches, procedural therapies (e.g., injections, nerve blocks), complementary therapies, and use of approved/cleared medical devices for pain management.

Table 1. Tools for patient risk assessment

Tool	Use	Who Administers?	Length
Current Opioid Misuse Measure (COMM)	Monitor for misuse by patients currently on long-term opioid therapy	Patient self-report	17 items
Diagnosis, Intractability, Risk, Efficacy (DIRE)	Screen for risk of opioid addiction	Clinician	7 items
Opioid Risk Tool (ORT)	Screen for risk of opioid addiction	Clinician or patient self-report	5 yes/no questions
Screener and Opioid Assessment for Patients with Pain, Version 1 and Revised (SOAPP, and SOAPP-R)	Screen for risk of opioid addiction	Patient self-report	24 items

Primary care clinicians should know about the range of treatment options available, the types of pain that may be responsive to those options, and when they should be used as part of a multidisciplinary approach to pain management.[37] Clinicians should also be aware that not all nonpharmacologic options have the same strength of evidence to support their utility in the management of pain, and some may be more applicable for some conditions than others.

Movement-based options

Movement therapies that may be helpful in patients with chronic pain include muscle-strengthening, stretching, and aerobic exercise (e.g., walking, aquatics). Recommended exercise programs typically occur one to three times a week for a total of 60-180 minutes per week, but any regimen must be carefully tailored to a patient's existing level of physical conditioning, comorbidities, and cognitive status.[38-40]

Additional movement-based options include:

- **Physical therapy** supervised by a licensed physical therapist, which can include resistance, aerobic, balance, and flexibility exercises as well as elements of massage, manipulation, or transcutaneous electrical nerve stimulation.
- **Tai chi**, a mind-body practice that combines controlled movements, meditation, and deep breathing. "Chair tai chi" can be an option for patients with limited mobility.
- **Yoga**, exercises or a series of postures designed to align muscle and bones, and increase strength and flexibility. It can also relax mind and body through breathing exercises and meditation. Gentler forms of yoga that may be more appropriate for older patients include Iyengar, Hatha, or Viniyoga.

Although these interventions may cause muscle soreness, increased back pain, or falls, movement-based options are generally considered safe.[40]

Weight loss

Some pain syndromes, such as knee osteoarthritis, are worsened by obesity. For some patients, pain due to this condition is improved by reducing body weight because of reduced loads and physical stresses on the affected joints. The goal of body weight reduction is a baseline weight loss of 7%-10% by calorie reduction and increased activity using a balanced diet with less than 30% of calories from fat, 15%-20% from protein, and 45%-60% from carbohydrates.[41]

Passive options

Acupuncture involves the stimulation of specific points on the body, most often involving skin penetration with fine metallic needles manipulated by hand but sometimes also including electrical stimulation or low intensity laser therapy. Potential adverse events include minor bruising and bleeding at needle insertion sites.[42]

Massage is the manual manipulation of the body to promote relaxation, reduce stress and improve well-being. Handheld devices may also provide relief for some patients. Some patients may report muscle soreness.[43]

Transcutaneous electrical nerve stimulation (TENS) is a machine that generates mild electrical pulses which are applied cutaneously. The electrical stimulation from TENS may block or disrupt pain signals to the brain, reducing pain perception. TENS machines can be used at home or in conjunction with other interventions like physical therapy.

Cognitive and behavioral options

Cognitive behavioral therapy (CBT) is a structured, time-limited (typically 3-10 weeks) intervention focused on how thoughts, beliefs, attitudes, and emotions influence pain and can help patients use their minds to control and adapt to pain. This therapy includes setting goals, often with recommendations to increase activity to reduce feelings of helplessness.[44]

Meditation

Mindfulness meditation programs typically include a time-limited (8 weeks; range 3-12 weeks) trainings with group classes and home meditation. The objective is to inculcate a long-term practice that helps patients refocus their minds on the present, increase awareness of self and surroundings, and reframe experiences.[45,46]

Non-opioid drug approaches

A wide range of medications can be used to treat pain, including:

- Acetaminophen
- NSAIDs (oral or topical)
- Antidepressants
  - serotonin and/or norepinephrine reuptake inhibitors
  - tricyclic antidepressants (TCAs)
  - selective serotonin reuptake inhibitors (SSRIs)
- Anticonvulsants
- Topical lidocaine or capsaicin
- Cannabinoid-based therapies
- Ketamine

Acetaminophen

Lower doses of acetaminophen are recommended to decrease risk of side effects. Patients should not exceed 1000 mg in a single dose. The maximum recommended dose for healthy adults is 4000 mg/day.[47]

The most severe potential side effect of acetaminophen is liver toxicity. Acetaminophen is the most common cause of acute liver failure, accounting for 46% of all cases.[48] Patients should stay within recommended doses to help prevent side effects and should only be prescribed one acetaminophen-containing product at a time.

NSAIDs

Chronic use of NSAIDs may be limited by gastrointestinal (GI) toxicity, including GI bleeding, upper GI symptoms, ulcers, and related complications. For high-risk patients, including the elderly, patients on warfarin or aspirin, and those with coagulopathies, adding a proton pump inhibitor (PPI) may help reduce the risk.[49,50] In addition to GI side effects, NSAIDs have been associated with an increased risk of renal and cardiac complications. Side effects with NSAIDs are typically lower with topical formulations.

Some early trials suggested that COX-2 inhibitors, as a class, were associated with higher risks for myocardial infarction and stroke compared to other NSAIDs, and the COX-2 inhibitor rofecoxib (Vioxx) was removed from the market in 2004 because of such concerns.[51] More recent trials and meta-analyses, however, provide strong evidence that the risks of CV events with celecoxib are no greater than those of other NSAIDs, and in 2018 two FDA advisory panels recommended that the FDA change its advice to physicians regarding celecoxib's safety.[52]

Selective serotonin norepinephrine reuptake inhibitors

SNRIs such as duloxetine, venlafaxine, and milnacipran are characterized by a mixed action on norepinephrine and serotonin, though their exact mechanism of action for pain reduction is unknown. These agents affect the descending pain pathways to facilitate pain relief. Side effects (e.g., nausea, dizziness, and somnolence) may limit treatment. Monitoring is suggested for blood pressure (duloxetine and venlafaxine), heart rate (venlafaxine), and drug interactions (duloxetine). SNRIs can be very helpful in patients who have central sensitization.

TCAs

TCAs inhibit reuptake of norepinephrine and serotonin. These agents act on descending pain pathways, but their mechanism of action for pain relief is unknown.

Examples of TCAs studied for the management of chronic pain include amitriptyline, desipramine, and nortriptyline. Side effects, such as anticholinergic effects (e.g., dry mouth, constipation, dizziness) and QTc prolongation limit the use of TCAs in elderly patients. The majority of side effects occur at the typically higher doses used to treat depression.

SSRIs

SSRIs, such as citalopram, fluoxetine, and paroxetine, block the reuptake of serotonin in the brain, making more serotonin available in the synapse. The mechanism of SSRIs for pain remains unknown. Compared to SNRIs and TCAs, there is relatively little evidence to support the use of SSRIs in treating chronic pain conditions.[28] Potential side effects of SSRIs include weight gain, sexual dysfunction, and QTc prolongation, especially with citalopram.

Anticonvulsants

Anticonvulsants, such as gabapentin, pregabalin, oxcarbazepine, and carbamazepine, are often prescribed for neuropathic pain and are thought to exert their analgesic effect by inhibiting neuronal calcium channels. Potential side effects include sedation, dizziness, and peripheral edema. Pregabalin and gabapentin have low abuse potential in the general population, are currently classified as Schedule V by the DEA, and prescriptions for these drugs are tracked by some state Prescription Drug Monitoring Programs (PDMPs). Anticonvulsants can be very helpful in patients who have central sensitization and neuropathic pain.

Topical lidocaine and capsaicin

Topical lidocaine inhibits the conduction of nociceptive nerve impulses. Irritation at the application site is the most common side effect. The most common products for chronic pain management are lidocaine 5% patches, available by prescription, and lidocaine 4% patches available OTC. Capsaicin is an active component of chili peppers and has moderate analgesic properties at 8% concentrations for neuropathic pain, specifically postherpetic neuralgia and diabetic neuropathic pain of the feet. [53] The most common side effect is a mild-to-severe burning sensation at the application site.

Cannabinoid preparations

With medical cannabis now legal in 36 states and recreational use legal in at least 10 states and the District of Columbia (as of 2020)[54], there has been increased interest among patients for the use of cannabis or cannabis derivatives (e.g., cannabidiol [CBD]) for pain relief. The CB1 and CB2 receptors have been shown to mediate the analgesic effects of cannabinoids[55] and some evidence suggests a potential benefit for chronic pain.

A 2017 National Academies of Science report, for example, concluded that "conclusive or substantial evidence" supports a beneficial role for cannabis or cannabinoids for treating chronic pain,[56] and a 2018 Cochrane review of the existing literature evaluating cannabinoids (cannabis, CBD, or combinations) suggests that these agents are moderately effective for neuropathic pain with adverse effects that are less than, or comparable to, existing non-opioid analgesics.[57]

But the evidence for a benefit of cannabinoids on acute pain, is extremely limited and mixed. A small double-blind, cross-over study in 18 females and experimentally-induced mild acute pain found no significant analgesic effect of oral cannabis extract.[58] Another randomized, double-blind study with 15 healthy volunteers using smoked cannabis found no analgesic effect with low doses of cannabis, a modest effect with moderate doses, and enhanced pain responses with high doses.[59] The authors of a 2017 review on cannabis and pain conclude that cannabis may have a narrow therapeutic window as a pharmacotherapy for chronic pain but that much more research is needed to inform physician recommendations to patients regarding the analgesic efficacy of cannabis.[60]

A systematic review of both randomized trials (47) and observational studies (57) in patients with chronic noncancer pain published through July 2017 found moderate evidence that cannabinoids can exert analgesia.[61] Cannabis preparations, however, may pose both short-term and long-term risks. Short-term effects include impaired memory, motor coordination, and judgment. Paranoid ideation and psychotic symptoms, while rare, may occur with high doses of THC. Possible long-term effects include impaired brain development in young adults, potential for habituation, and increased risk of anxiety or depression. Abrupt cessation of marijuana in long-term users may cause withdrawal symptoms such as anxiety, irritability, craving, dysphoria, and insomnia. There is an increased risk of chronic bronchitis, respiratory infections, and pneumonia with inhaled products.[62]

Nonetheless, the use of cannabis may have an opioid-sparing effect at a population level. The use of medical cannabis has been associated with a 25% reduction in opioid overdose mortality in states that legalized medical use.[63] However, a more recent study showed that states legalizing medical cannabis actually experienced a 22.7% increase in opioid overdose deaths.[64]

FDA-approved cannabinoids include dronabinol (Marinol), indicated for second-line treatment of chemotherapy-induced nausea and vomiting, and anorexia-associated weight loss in patients with HIV. Nabilone (Cesamet) is indicated for chemotherapy-induced nausea and vomiting. Common side effects include dizziness/vertigo and euphoria. Dronabinol may cause nausea/vomiting, abdominal pain, and abnormal thinking. Nabilone may cause ataxia and dry mouth.[62,65,66] None of these are indicated for the treatment of pain. When recommending cannabis for patients with chronic pain, clinicians may inform patients that the analgesic properties are due to both the CBD and THC components, which act on different pain pathways.[67]

Ketamine

Ketamine has been used as a general anesthetic since the 1960s, but its use in subanesthetic concentrations for analgesia has grown rapidly in recent years, due, in part, to efforts to reduce the risks of chronic opioid use.[68] Ketamine has been successfully used to treat such acute pain conditions as sickle cell crises, renal colic, and trauma.[68] Recently the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists released the first joint recommendations for subanesthetic ketamine (including transdermal ketamine) for acute pain.[68]. Ketamine infusions are used for the treatment of complex regional pain syndrome based on placebo-controlled trials, and topical ketamine may also be beneficial for the cutaneous hypersensitivity associated with this condition.[69]

Opioids

Mechanism of Action

Opioids exert their analgesic effects by acting on the mu, kappa, and delta opioid receptors. Individual agents may be classified as agonists or partial agonists of those receptors:[70]

- Agonists (e.g., morphine, codeine, hydromorphone, hydrocodone) stimulate at least one of the opioid receptors and provide continued analgesia with increasing doses.
- Partial agonists (e.g., buprenorphine) have high affinity at mu-receptors, have a ceiling for analgesic effect, and are less likely to cause respiratory depression.

Opioids are classified by the Drug Enforcement Agency (DEA) according to their presumed abuse and addiction potential, although the evidence base for making these differentiations continues to evolve. Tramadol, for example, is now known to have as much potential for abuse as opioids in more restrictive classes, although its DEA classification has not changed.[71]

Relative effectiveness

The analgesic efficacy of opioids for treating acute pain has been known for centuries and they continue to be reliable agents for moderate-to-severe acute pain, although they are not without risks. But the evidence for opioid efficacy for acute pain cannot be extended to chronic pain with a few exceptions that are discussed below. Neuronal and physiologic adaptations to long-term opioid use can result in reduced analgesic effectiveness, or even, paradoxically, increased pain or sensitivity to pain.[72] Opioid-induced hyperalgesia is different pharmacologically from the phenomenon of opioid tolerance, although both can lead to an increased need for opioids and disentangling the two, clinically, can be difficult.[73]

For chronic pain, the evidence that opioids reduce pain and improve function more than placebo is relatively weak. A 2018 systematic review and meta-analysis of 96 trials comparing various opioids vs. placebo or non-opioid analgesics in 26,169 patients with chronic noncancer pain found that opioids may slightly reduce pain and increase physical functioning compared to placebo, but not compared to non-opioids.[12] In 76 trials comparing opioids vs. placebo with follow-up ranging from 1 to 6 months, the reduction in pain scores with opioids (on a 10-point scale) was only 0.69 points, which is below the generally-accepted 2-point minimum clinically important difference for pain. Physical function scores (on a 100-point scale) improved with opioids by 2.04 points, which, again, may not be clinically important. The risk of vomiting with opioids, however, was more than 4 times higher than with placebo.[12]

The same meta-analysis compared opioids to non-opioid analgesics including NSAIDs, TCAs, anticonvulsants, and synthetic cannabinoids. No significant differences were found in physical functioning scores for any of the comparisons, and no significant differences were found in pain scores for comparisons with NSAIDs, TCAs, or cannabinoids.[12]

Exceptions: chronic opioid use in limited patient subsets

Sickle cell disease as an example for which chronic opioid therapy may be appropriate in some patients. The risk for opioid death in patients with sickle cell disease comprises a small fraction of the total number of opioid-related deaths.

From 1999 through 2013, there were 174,959 documents deaths attributed to opioid use. Of these 174, 959 deaths, 95 were patients with sickle cell disease (0.05%).[74] The pain experienced by patients includes both acute and chronic aspects through multiple mechanisms that are not completely understood. The American Society of Hematology 2020 guidelines endorses the use of chronic opioid therapy for patients with sickle cell disease with pain that is refractory to multiple other treatments using the lowest effective dose and with regular monitoring.[75,76]

Opioid formulations

Prescription opioids are available in immediate-release and extended-release/long-acting (ER/LA) formulations. Immediate-release agents are recommended in opioid-naïve patients and for all acute pain conditions, with ER/LA agents reserved for patients or conditions in which the longer duration of action and smoother pharmacodynamics are preferred.[31] A trial comparing immediate release to an ER/LA opioid did not find evidence that the continuous, time-scheduled use of ER/LA opioids was more effective or safer than intermittent use of the immediate-release opioid.[71]
According to the FDA, ER/LA opioids should only be used for patients who tolerate 60 morphine milligram equivalents per day (MMED) for at least one week.[78]

Efforts to create formulations with lower risks of abuse have met with limited success. For example, ER Oxymorphone was removed from the market after reports of intravenous abuse of the oral formulation.[79] Abuse-deterrent or tamper-resistant formulations do not prevent patients from developing opioid dependence, opioid use disorder, or simply taking too much of an opioid by mouth.[80,81]

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

Atypical opoids: tramadol and tapentadol

Tramadol and tapentadol are mu receptor agonists and norepinephrine reuptake inhibitors. Their mechanisms of action are unknown, but their analgesic effects are similar to morphine. Patients taking tramadol should be monitored for nausea, vomiting, constipation, and drowsiness, all of which are similar to side effects with opioids.[82] There is potential risk of serotonin syndrome when tramadol is combined with SSRIs, SNRIs, or tricyclic antidepressants.[83]

As noted above, tramadol is classified as Schedule IV, which has led some to view it as less potent or safer than other opioids. The 2016 National Survey on Drug Use and Health, however, found that 1.7 million people in the U.S. aged > 12 years reported misusing tramadol products (e.g., Ultram, Ultram ER, Ultracet) in the previous year.[71] In addition, a 2019 cohort study of 88,902 patients with osteoarthritis showed increased risks of death at one year compared to NSAIDs naproxen, diclofenac, and celecoxib.[84]

Abrupt cessation of tramadol is associated with opioid withdrawal, restlessness, and drug cravings (similar to those associated with other opioids) as well as hallucinations, paranoia, extreme anxiety, panic attacks, confusion, and numbness/tingling in extremities (which are less typical of other opioids).[85]

Tapentadol is FDA-approved for treating neuropathic pain associated with diabetic peripheral neuropathy, although it is also used for musculoskeletal pain. A 2015 Cochrane review of 4 randomized trials with 4,094 patients with osteoarthritis or back pain found modest reductions in pain with tapentadol vs. placebo.[86]

Problematic opioid use

Although evidence for the long-term effectiveness of opioids for chronic pain is weak, evidence for opioid-related harms is abundant and strong. In a 2007 study assessing behaviors indicative of opioid misuse, many patients in primary care practices reported having engaged in aberrant behaviors with opioids one or more times (Table 2).[9] It is important to recognize and differentiate problematic use from adverse side effects of opioids. For instance, tolerance and opioid withdrawal occur with long term use of prescribed opioids. Clinicians should be able to differentiate this from problematic use.

Among adults without a prescription, 41% obtained prescription opioids from friends or relatives for their most recent episodes of misuse.[87]

For prescription opioids, long-term therapy is associated with an increased risk in accidental overdose and death. A retrospective study including 9,940 patients who received three or more opioid prescriptions within 90 days for chronic pain between 1997 and 2005 found that annual overdose rates rose significantly as doses exceeded 50 MMED (Figure 4).[88]

Combining opioids with sedating drugs such as benzodiazepines or alcohol increases the risk of respiratory depression and overdose death.[34] Benzodiazepines have been linked with overdose fatalities in 50-80% of heroin overdoses, and 40-80% in methadone-related deaths.[34,89] Patients prescribed benzodiazepines who are being initiated on opioids should have their benzodiazepine tapered and discontinued whenever possible. For patients being co-managed by mental health professionals, coordinate a plan regarding continuing or tapering benzodiazepines in the setting of opioid co-prescribing.

Case Study 2

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

Wayne is an 86-year-old who lives at home with his wife. He was diagnosed with ALS 6 months ago, with deterioration occurring first in his diaphragm. He has been experiencing increasing muscle weakness in his legs and uses a walker or a wheelchair to get around in his home. He uses a bilevel positive airway pressure device except when eating or bathing and finds it helpful. He takes the following medications: fish oil, a statin, a thiazide diuretic, and a non-benzodiazepine sedative to help him sleep. Lately he has been complaining of pain and stiffness in both of his knees and hips, which interferes with his sleep. He is physically deconditioned due to a lack of exercise, and has become increasingly withdrawn socially, which worries his wife and family members. He asks if you can prescribe something to ease his pain.

1. **Is Wayne a good candidate for an ER/LA opioid? Why, or why not?**

2. **Is he a better candidate for an immediate-release opioid? Why or why not?**

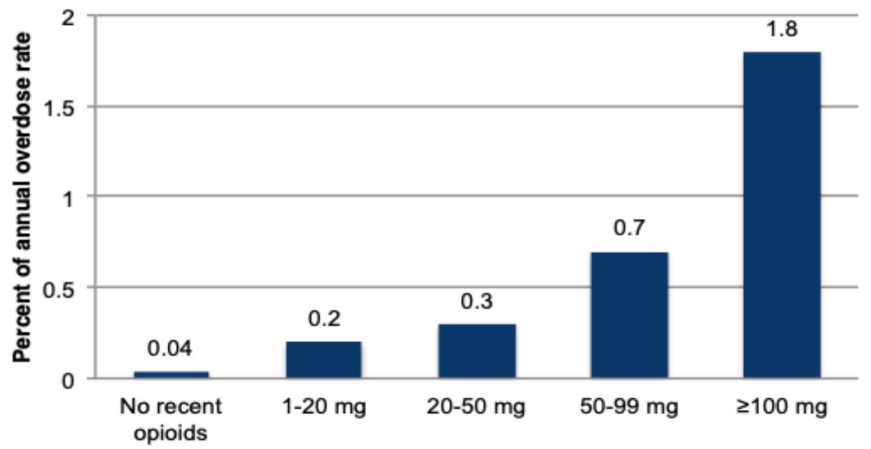
3. **Would Wayne's current medication need to be adjusted if he were to be prescribed an ER/LA opioid?**

4. **What kinds of non-opioid treatments might be tried to help Wayne with his pain?**

Table 2. Behaviors indicative of opioid misuse[9]

Behavior	Frequency in patients with opioid misuse
Requested early refills	47%
Increased dose on own	39%
Felt intoxicated from pain medication	35%
Purposely over sedated oneself	26%
Used opioids for purpose other than pain	18%

Figure 4. Risk of overdose rises with daily milligram morphine-equivalent dose.[88]



Other adverse events

In addition to risks of misuse, addiction, respiratory depression, and overdose death, there are many well-known side effects associated with chronic opioid use that can significantly compromise quality of life, including constipation, nausea or vomiting, sedation, pruritus, erectile dysfunction, menstrual changes, fracture, immunosuppression, hallucinations, and hyperalgesia.

Gastrointestinal side effects

Constipation is one of the most common opioid-related adverse events, affecting most patients to at least some degree, and which usually does not resolve with continued exposure.[28] To mitigate this side effect, patients should use a mild stimulant laxative such as senna or bisacodyl and increase the dosage in 48 hours if no bowel movement occurs. Physicians should perform a rectal examination if no bowel movement occurs in 72 hours. If there is no impaction, consider other therapies such as an enema, suppository, or magnesium citrate.[90]

Medications for refractory, opioid-induced constipation include naloxone derivatives: naloxegol (Movantik), methylnaltrexone (Relistor), or naldemedine (Symproic). Naloxegol is an oral tablet that is used daily while methylnaltrexone is a subcutaneous injection or oral tablet used daily. Naldemedine is taken by mouth daily (0.2 mg) and may cause side effects such as abdominal pain or discomfort, diarrhea, and nausea.[88] In the COMPOSE-1 trial, patients on naldemedine had significantly more spontaneous bowel movements (defined as ≥3 per week) than those on placebo (47.6% vs. 34.6%, P=0.002).[91]

For nausea or vomiting, physicians should consider a prophylactic antiemetic, add or increase non-opioid pain control agents (e.g., acetaminophen as an opioid-sparing drug), and decrease opioid dose by 25% if analgesic is satisfactory.

Sedation

Sedation is the first warning sign of a patient being at risk for opioid overdose. Take this symptom very seriously. If a patient complains of sedation, determine whether sedation is related to the opioid, eliminate nonessential depressants (such as benzodiazepines or alcohol), reduce dose by 10%-15% if analgesia is satisfactory, add or increase non-opioid or non-sedating adjuvant for additional pain to reduce opioid dose. There is insufficient evidence to recommend opioid rotation as a possible means of reducing sedation.[31] Patients should also be co-prescribed naloxone for opioid overdose reversal.

Fracture

A retrospective cohort study over seven years compared the risk of fracture associated with starting opioids vs. NSAIDs (2,436 older adults initiated on opioids and 4,874 older adults initiated on NSAIDs). Opioids significantly increased the risk of fracture in a dose-dependent fashion. The opioid formulation mattered with much of the risk in the first month after drug initiation for short-acting opioids, though fracture increased for both long- and short-acting opioids over time.[92]

Infection

Opioids may increase risk of infection in older adults. A case-control study of 3,061 older community dwelling adults ages 64-95 years evaluated the association between pneumonia and opioid use. Current prescription opioid users had a 38% increased risk of pneumonia compared with nonusers. The risk was highest for opioid users categorized as being immunosuppressed, such as those with cancer, recent cancer treatment, or chronic kidney disease, or those receiving immunosuppressive medications or medications for HIV.[93]

Myocardial Infarction (MI)

A case-control study assessed the risk of MI among adults on opioids for chronic pain in the UK General Practice Research Database (11,693 cases with up to four matched controls). Current opioid use was associated with a 28% increased risk of MI compared to non-use.[94]

Erectile Dysfunction (ED)

In a cross-sectional analysis of 11,327 men with back pain, 909 (8%) were receiving ED medications or testosterone (documented between 6 months before and 6 months after the study index visit). Prescriptions for an ED drug or testosterone were 54% greater for men using doses ≥120 MMEDs compared with those using doses of 1 to <20 MMED. In addition, the proportion of men receiving either of types of medications was 95% greater for those with chronic opioid use compared with those with no opioid use. These findings suggest that dose and duration of opioid use are associated with ED.[95]

Tamper-resistant/abuse-deterrent opioids

One strategy to mitigate the risk of opioid abuse has been the development of "abuse-deterrent" formulations of opioids that make it more difficult to alter for non-oral consumption (e.g., injecting, snorting, or smoking).[96] However, these opioids are more aptly named as "tamper-resistant" formulations instead of "abuse-deterrent" since they are no less potentially addictive than regular opioids when taken by mouth.

Tamper-resistant formulations often contain a higher opioid dose than immediate-release preparations. Furthermore, most are extended-release and also considerably more expensive than generic, off-patent opioids.[96] As of this writing, only one immediate-release opioid is available in an abuse deterrent formulation (oxycodone hydrochloride [RoxyBond]).[96]

Patient education

Before prescribing an opioid for pain, clinicians should discuss with patients the risks and benefits of such therapy. An important consideration in framing treatment, and a key message to communicate to patients, is that the goal is not "zero pain" but, rather, a level of analgesia that maximizes a patient's physical and mental functioning.[97] A multi-modal approach, using both drug and non-drug treatments, should be encouraged.

In addition, patients should be educated about the safe storage and disposal of opioid medications. Safe use means following clinician instructions about dosing, avoiding potentially dangerous drug interactions (e.g., alcohol), and assuring full understanding of how the medication should be consumed or applied. Remind patients that opioid pain medications are sought after by many people, and, therefore, opioids should be stored in a locked cabinet or, if a locked unit is not available a place that is not obvious or easily accessed by others.

Proper disposal methods should be explained:

- Follow any specific disposal instructions on the prescription drug labeling or patient information that accompanies the medication
- Do not flush medicines down the sink or toilet unless the prescribing information specifically instructs to do so.
- Return medications to a pharmacy, health center, or other organization with a take-back program.
- Mix the medication with an undesirable substance (e.g., used coffee grounds or kitty litter) and put it in the trash, or use special drug deactivation pouches that your health care provider may recommend.

Managing acute pain

It is now becoming clear that many of the problems and risks associated with managing chronic pain with opioids are also at work in the management of acute pain with opioids. For example, a number of studies demonstrate increased risk of new persistent opioid use in opioid-naïve patients after having been prescribed opioids for acute pain.[98-101] Although the risk of opioid misuse in patients prescribed opioids for acute post-surgical or post-procedural pain is relatively small (roughly 0.6% per year)[102], the volume of such procedures (approximately 48 million ambulatory surgeries or procedures in 2010)[103] translates into large numbers of patients (i.e., approximately 160,000) who may develop dependence, abuse, or overdose every year.

A central tenet of pain management, whether acute or chronic, is that the goal of treatment is a tolerable level of pain that allows the patient maximum physical and emotional functioning with the lowest risk of side effects, progression to chronic pain, or misuse or abuse[104] This requires an adroit balancing of patient-related factors (e.g., comorbidities, medical history, risk of abuse) and drug-related factors (e.g., potency, mechanism of action, expected side effects). A commonly-recommended way to achieve this balance is with multimodal analgesia, in which several therapeutic approaches are used, each acting at different sites of the pain pathway, which can reduce dependence on a single medication and may reduce or eliminate the need for opioids and attendant risks/side effects.[105]

Multimodal analgesia (e.g., using drugs from two or more classes, or a drug plus a non-drug treatment) can produce synergistic effects, reduce side effects, or both. One example of multimodal analgesia is the use of both an NSAID and acetaminophen, plus physical approaches (e.g., cold, compression, or elevation) to manage postoperative pain. Demonstrated benefits of multimodal analgesia include earlier ambulation, earlier oral intake, and earlier hospital discharge for postoperative patients, as well as higher levels of participation in activities necessary for recovery (e.g., physical therapy).[105]

Non-pharmacological treatments for acute pain

When possible, non-pharmacologic methods should be used, alone or in combination with analgesics, to manage acute pain.[106] The degree to which this is possible depends on the severity, type, and origin of the pain, but many non-pharmacological approaches can be very effective and their use avoids the potential side effects and risks associated with pharmacological interventions.

Physical methods of pain management can be helpful in all phases of care, including immediately after tissue trauma (e.g., rest, application of cold, compression, elevation) and later in the healing period (e.g., exercises to regain strength and range of motion).

Physical therapy may be useful for a range of musculoskeletal issues and can be helpful in recovering from acute pain-producing traumas initially treated with other methods. A 2018 study reported that patients with low back pain who first consulted a physical therapist were less likely to receive an opioid prescription compared to those who first saw their primary care physician.[107]

Exercise therapy can take many forms, including walking, swimming or in-water exercise, weight training, or use of aerobic or strength-training equipment. According to a CDC review, conditions that may improve with exercise therapy include low back pain, neck pain, hip and knee osteoarthritis pain, fibromyalgia, and migraine.[108]

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

Case Study 3

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

Hannah, a 64-year-old female presents with severe pain in both anterior-lateral thighs and lateral shoulders, rated at 7/10 on the VAS. She reports that the pain is constant and that she gets only mild relief from NSAIDs. She cannot walk without a cane or walker. She had been diagnosed six years ago with severe peripheral neuropathy in her legs for which she was prescribed gababentin. She reports that gababentin gives her intense "brain fog" and forgetfulness, however, and that she has stopped taking it because of these side effects. The patient also has type 2 diabetes, initially treated with metformin but lately also with 50 units of insulin per day.

The patient was given a treatment plan that included chiropractic adjustments and exercise rehabilitation exercises. She also adopted a "Paleo" diet, which she followed strictly for three months, although it did not significantly lower her hemoglobin A1c levels. She has come to you because the pain is eroding her quality of life, interrupting her sleep, and contributing to tensions with her partner.

1. **Given the subjective nature of pain, how can a clinician more objectively assess the kind of pain reported by patients such as this?**

2. **Is it reasonable to believe that the gabapentin was responsible for her reported side effects?**

3. **Would Hannah be a good candidate for an opioid analgesic? Why or why not?**

4. **What non-pharmacological treatments might be tried for reducing this patient's pain?**

Non-opioid pharmacologic treatments for acute pain

Acetaminophen and NSAIDs

In general, mild-to-moderate acute pain responds well to oral non-opioids (e.g., acetaminophen, NSAIDs, and topical agents). Although they are weaker analgesics than opioids, acetaminophen and NSAIDs do not produce tolerance, physical dependence, or addiction and they do not induce respiratory depression or constipation. Acetaminophen and NSAIDs are often added to an opioid regimen for their opioid-sparing effect. Since non-opioids relieve pain via different mechanisms than opioids, combination therapy can provide improved relief with fewer side effects.

The choice of medication may be driven by patient risk factors for drug-related adverse effects (e.g., NSAIDs increase the rate of gastrointestinal, renal, and cardiovascular events). If acetaminophen or NSAIDs are contraindicated or have not sufficiently eased the patient's pain or improved function despite maximal or combination therapy, other drug classes (e.g., opioids) are sometimes used.

Non-opioid analgesics are not without risk, particularly in older patients. Potential adverse effects of NSAIDs include gastrointestinal problems (e.g., stomach upset, ulcers, perforation, bleeding, liver dysfunction), bleeding (i.e., antiplatelet effects), kidney dysfunction, hypersensitivity reactions, and cardiovascular concerns, particularly in the elderly.[109] The threshold dose for acetaminophen liver toxicity has not been established; however, the Food and Drug Administration (FDA) recommends that the total adult daily dose not exceed 4,000 mg in patients without liver disease (with a lower ceiling for older adults with certain conditions).[110]

The FDA currently sets a maximum limit of 325 mg of acetaminophen in prescription combination products (e.g., hydrocodone and acetaminophen) in an attempt to limit liver damage and other potential ill effects of these products.[32]

Topical agents

Topical capsaicin and salicylates can both be effective for short term cutaneous pain relief and generally have fewer side effects than oral analgesics, but their long-term efficacy is not well studied.[111,,112] Topical aspirin, for example, can help reduce pain from acute herpes zoster infection.[107] Topical NSAIDs and lidocaine may also be effective for short-term relief of superficial pain with minimal side effects. Topical agents can be simple and effective for reducing pain associated with wound dressing changes, debridement of leg ulcers, and other sources of superficial pain.[103]

Anticonvulsants

Anticonvulsants, such as gabapentin, pregabalin, oxcarbazepine, and carbamazepine, are often prescribed for chronic neuropathic pain (e.g., post-herpetic neuralgia and diabetic neuropathy) although evidence for efficacy in acute pain conditions is weak.[114] A 2017 trial, for example, randomized 209 patients with sciatica pain to pregabalin 150 mg/day titrated to a maximum of 600 mg/day vs. placebo for 8 weeks.[115] At 8 weeks there was no significant difference in pain between groups (mean leg pain intensity on a 0-10 scale 3.7 with pregabalin vs. 3.1 with placebo, P=0.19).

Opioids for acute pain: use caution

Opioids are commonly prescribed for pain, with nearly two thirds (64%) of the public reporting being prescribed an opioid for pain at some point in their lives.[116] However, this approach is not as safe and effective as once thought, and high-dose prescriptions or prolonged use not only increase the risk of misuse, addiction, or overdose, they may actually *increase* pain and pain sensitivity.[117,118]

Recent evidence suggests that opioids may not be more effective for moderate to severe acute pain than non-opioid pain regimens.[119,120] A randomized trial of 416 patients with acute extremity pain found no clinically important differences in pain reduction at two hours after single-dose treatment with ibuprofen and acetaminophen vs. three different opioid and acetaminophen combination analgesics.[113]

Physical dependence can readily occur after use of opioids at a sufficient dose (e.g., 30mg of oxycodone) for just a few days. In addition, side effects of opioid use can include constipation, confusion/gait instability, respiratory depression, pruritus, erectile dysfunction, and fractures, all of which may be more problematic in older patients and occur at higher rates than with non-opioid analgesics.

A cross-sectional study compared common side effects experienced during the first week of treatment with opioid analgesics vs. non-opioid analgesics in patients over age 65 with acute musculoskeletal pain.[121] The intensity of six common opioid-related side effects were significantly higher with opioids. (A limitation of this study is that it could not assess severe but less common adverse events associated with NSAIDs and acetaminophen, including the risk for gastrointestinal bleeding, acute kidney injury, and hepatotoxicity.)

In a retrospective study of 12,840 elderly patients with arthritis, opioid use was associated with an increased risk relative to non-opioids for cardiovascular events, fracture, events requiring hospitalization, and all-cause mortality.[122]

The risk of prolonged opioid use is particularly high after arthroscopic joint procedures. In a 2019 case-control study of 104,154 opioid-naïve adults, 8,686 (8.3%) developed new prolonged opioid use (continued opioid use between 91 and 180 days after shoulder arthroscopy).[123]

Subgroups at higher risk for long-term use included women, those with a history of alcohol use disorder, those with a mood disorder, and those with an anxiety disorder.

Opioid choices for acute pain

If an opioid is deemed necessary to treat moderate-to-severe acute pain, the following general principles are recommended when starting an opioid:

- Avoid extended-release and long-acting opioids such as methadone, fentanyl patches, and ER/LA versions of opioids such as oxycodone or oxymorphone.
- Avoid co-prescribing opioids with other drugs known to depress central nervous system function (e.g., benzodiazepines)
- Limit the dose and quantity of opioids to address the expected duration and severity of pain (usually less than 7 days).
- Combine opioids with other treatments (e.g., non-pharmacologic options such as exercise or cognitive behavioral therapy, NSAIDs, or acetaminophen).
- Closely monitor patients with impaired hepatic or kidney function if they are prescribed opioids, and adjust the dose or duration accordingly

Immediate-release agents are strongly preferred because of the higher risk of overdose associated with ER/LA agents. A cohort study of 840,000 opioid-naïve patients over a 10-year span found that unintentional overdose was 5 times more likely in patients prescribed ER/LA agents compared to immediate-release opioids.[124]

Opioid dosing for acute pain

The amount of opioid prescribed should relate to the level of pain expected from the injury or procedure. Injuries or procedures involving bones and joints tend to be more painful than those involving soft tissues.[125] Table 3 illustrates the wide range of expected pain and associated recommended opioid doses for some common surgeries or procedures.

Table 3. Opioid dose recommendations for post-procedural pain[126]	
Procedure	Number of oxycodone 5 mg tablets (or equivalent)
Dental extraction	0
Thyroidectomy	5
Breast biopsy or lumpectomy	5
Lumpectomy plus sentinel lymph node biopsy	5
Hernia repair (minor or major)	10
Sleeve gastrectomy	10
Prostatectomy	10
Open cholecystectomy	15
Cesarean delivery	15
Hysterectomy (all types)	15
Cardiac surgery via median sternotomy	15
Open small bowel resection	20
Simple mastectomy with or without sentinel lymph node biopsy	20
Total hip arthroplasty	30
Total knee arthroplasty	50

Managing chronic non-cancer pain

Management of chronic non-cancer pain begins by establishing individualized treatment goals, exploring non-opioid treatment options, and addressing comorbid depression and anxiety, if present. Pain management goals may include both pain and functional targets, with the understanding that being 100% pain free is not realistic. Functional goals should focus on activities that are meaningful to the patient and attainable based on the severity of the painful condition. Multi-modal approaches that include non-drug (procedures, integrative treatments) and drug interventions are recommended.[28]

Be aware that comorbid conditions such as depression and anxiety can impact pain management. (In a study of 250 patients with chronic pain and moderate depression, using antidepressant therapy reduced pain levels before analgesic interventions were added.[127])

For patients with intractable, moderate-to-severe chronic noncancer pain unresponsive to non-opioid treatment options, a trial of opioids may be indicated guided by the following principles (each detailed below):

- Discuss risks and benefits of opioid use
- Establish a written treatment agreement
- Check or monitor opioid use with the prescription drug monitoring program
- Use caution with dose escalation
- Prescribe naloxone if at risk for overdose
- Screen for opioid misuse or abuse using history and, ideally, a validated questionnaire, as well as urine drug testing
- Taper or discontinue opioids when possible

Establishing a written treatment agreement

Written documentation of all aspects of a patient's care, including assessments, informed consent, treatment plans, and provider/patient agreements, are a vital part of opioid prescription "best practices." Such documentation provides a transparent and enduring record of a clinician's rationale for a particular treatment and provides a basis for ongoing monitoring and, if needed, modifications of a treatment plan.[104]

Many computerized systems are now available for the acquisition, storage, integration, and presentation of medical information. Most offer advantages that will benefit both patients and prescribers, such as maintaining up-to-date records, and providing instant availability of information relevant to prescribing or treatment. Although automation can help, clear documentation is not dependent on electronic record-keeping; it merely requires a commitment to creating clear and enduring communication in a systematic fashion. Good documentation can be achieved with the most elaborate electronic medical record systems, with paper and pen, or with dictated notes. Clinicians must decide for themselves how thoroughly, and how frequently, their documentation of a patient's treatment should be.

Informed Consent

Informed consent is a fundamental part of planning for any treatment, but it is particularly important in long-term opioid therapy, given the potential risks of such therapy. At its best, consent also fortifies the clinician/patient relationship.

Prescribers must be able to answer with confidence four key questions when obtaining informed consent in the context of treatment with opioids:[122]

1. Does the patient understand the various options for treatment?
2. Has the patient been reasonably informed of the potential benefits and risks associated with each of those options?
3. Is the patient free to choose among those options, free from coercion by the healthcare professional, the patient's family, or others?
4. Does the patient have the capacity to communicate his or her preferences—verbally or in other ways (e.g., if the patient is deaf or mute)?
5. Is there a proxy available if the patient cannot provide consent due to cognitive impairment?

Documentation related to these key areas can be accomplished by creating a separate paper or electronic informed consent form or by incorporating informed consent language into a larger treatment plan or patient/provider agreement.

Patient-Provider Agreements

A written agreement between a clinician and a patient about the specifics of their pain treatment with opioids can help clarify the plan with the patient, the patient's family, and other clinicians who may become involved in the patient's care.[104]

Such agreements can also reinforce expectations about the appropriate and safe use of opioids. Caution must be exercised, however, to ensure that patient/provider agreements are not used in a coercive way to unethically place patients in the position of having to agree to its terms or else lose an important component of their treatment (or even lose *all* treatment).[128]

Although evidence is lacking about the most effective methods to convey the information included in most patient-provider agreements, such agreements have been widely used and are recommended by regulators and many experts on treatment guidelines for long-term opioid therapy.[28] The Veterans Administration and U.S. Department of Defense chartered an expert panel to undertake a systematic review of existing medical literature on this subject. In the clinical practice guidelines resulting from that work, the panel concluded that opioid treatment agreements are a standard of care when prescribing long-term opioid therapy.[128]

Clinicians should strive to craft agreements that serve their patients' best interests and avoid coercive or punitive language. Thus, agreements should avoid:

1. Putting all burden on the patient rather than sharing it between patient and clinician
2. Framing the agreement in terms of punishments for possible future crimes or difficulties

3. Using language that is stigmatizing, dominating, or pejorative
4. Using coercion in any way
5. Imposing limitations for the clinician's convenience without clear and substantial benefit for the patient.
6. Insisting on behaviors unrelated to actual use of medications Using the term "fired" to describe termination of treatment.
7. Threatening abandonment or suggesting that patients will not have continued access to non-opioid pain-relieving treatments if opioids are terminated

To be effective, written agreements must be clearly understood by the patient. This may require the provision of agreements in multiple languages. All agreements should be written at the sixth- to seventh-grade level or even lower.[129] Translators may need to be provided for speakers of other languages to ensure patient understanding and effective informed consent. A patient who does not fully understand the potential risks and benefits of a treatment cannot be truly "informed" as required by the legal and ethical guidelines for medical practice. Time must be allowed for patients to ask questions, and for prescribers to ensure patients understand what they are being told. Some, or all, of these tasks may be handled by trained personnel (or staff members) rather than clinicians.

Although the term "agreement" is generally perceived as being more patient-friendly than the word "contract," clinicians should understand that, from a legal standpoint, any written or oral agreement between a prescriber and a patient may be considered a binding "contract."[130] Clinicians should ensure that the terms in any agreement are understood by the patient, and are acceptable, attainable, and consistent with high-quality practice.

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

Creating individualized function-based pain treatment plans

Once a patient has been assessed and accepted as a candidate for chronic opioid therapy, and after informed consent has been obtained for such treatment, a written plan for implementing the treatment should be drafted. Such plans typically include a statement of the goals of therapy. These goals should be written carefully in light of the inherent subjectivity of pain. Since pain itself cannot be measured objectively, framing treatment goals solely in terms of pain relief means that such goals cannot be objectively confirmed.

Although a patient's subjective pain and suffering are obviously important factors, only the functional impact of the pain can be measured and used to create objective treatment goals. This impact takes many forms, but typically chronic pain erodes foundations of daily life, such as physical activity, concentration, emotional stability, interpersonal relationships, and sleep. This can, in turn, degrade functioning at work or in the home, which can lead to depression, anxiety, insomnia, and even suicide. Clinicians should know that even relatively modest reductions in pain can translate into significant functional improvements as pain rating declines.[104] A 20% reduction in a pain score (i.e., roughly two points on the standard 0-10 pain scale) may be acceptable if it produces significant functional benefits for a patient.

Framing treatment goals in terms of improved patient functioning, rather than merely pain relief, offers two primary advantages to clinicians:

- Prescribing decisions (or decisions to terminate treatment) are based on outcomes that can be objectively demonstrated to both clinician and patient (and, possibly, to the patient's family)
- Individual differences in pain tolerance become secondary to the setting and monitoring of treatment goals, since subjectively perceived levels of pain are not the primary focus in determining functionality.

Basing treatment plans on functional goals is especially valuable in the context of prescribing opioid pain medications, because such goals may help determine whether a patient has an opioid use disorder because patients with OUD often have decreased functioning, while effective pain relief typically improves functioning.

Functional decline itself may result from a range of problems, including inadequate pain relief, non-adherence to a regimen, function-limiting side effects, or untreated affective disorders. Sometimes impaired functioning is the result of OUD, and these objective results may shed valuable light on an otherwise confusing presentation of a patient's pain symptoms.

Functional treatment goals should be realistic. Progress in restoring function is usually slow and gains are typically incremental. Chronic non-cancer pain is often marked by long-standing physical and psychological deconditioning, and recovery may require reconditioning that may take weeks, months, or years. It is much better to set goals that are slightly too low than slightly too high. Raising goals after a patient has "succeeded" in achieving them is far more motivational and encouraging than lowering goals after a patient has "failed." Table 4 illustrates some simple functional goals and ways they might be verified.

The responsibility for obtaining evidence of success in meeting a functional goal lies with the patient and should be made explicit in the prescribing agreement. If a patient is unable to document or achieve the progress outlined in a treatment plan, this may suggest a need for goal readjustment.

Initiating therapy

When initiating a trial of opioids, start with immediate-release formulations because their shorter half-life reduces the risk of inadvertent overdose. Prescribe low doses on an intermittent, as-needed basis. For elderly patients who have comorbidities, start at an even lower dose (25-50% of usual adult dose).

Long-term opioid use often begins with treatment for acute pain, and research shows that opioids are often over-prescribed for acute pain. For example, a study of 1,416 patients in a 6-month period found that surgeons prescribed a mean of 24 pills (standardized to 5 mg oxycodone) but patients reported using a mean of only 8.1 pills (utilization rate 34%).[125] For acute pain, only enough opioids should be prescribed to address the expected duration and severity of pain from an injury or procedure (or to cover pain relief until a follow-up appointment). Several guidelines about opioid prescribing for acute pain from emergency departments[131,132] and other settings[133,134] have recommended prescribing $\leq$ 3 days of opioids in most cases, whereas others have recommended $\leq$ 7 days,[135] or $\leq$ 14 days.[136] CDC guidelines suggest that for most painful conditions (barring major surgery or trauma) a 3-day supply should be enough, although many factors must be taken into account (for example, some patients might live so far away from a health care facility or pharmacy that somewhat larger supplies might be justified) and clinician judgment is an important factor in determining the supply.[31]

Monitoring opioid use

Follow-up appointments should occur one to four weeks after initiation of opioids or with dose changes; maintenance therapy visits should occur at least every three months. Each visit should include an assessment using a pain and function tool, questions about side effects, evaluation of overdose risk, and discussions about how the medication is being used.[34]

Many strategies to monitor opioid use and ensure patient safety have been recommended. However, simply asking patients how they are using the medication, how often they take it, how many pills they take at one time, and what triggers them to take the medication, can identify patients who may be misusing opioids or need changes to their pain management plan.

Case Study 4

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

Inessa is 72 and lives in an urban area, having immigrated from Russia as a young woman. She grew up on a farm and worked in the fields or tending animals starting as a child. She blames these early labors for the arthritis she now has in her hands and wrists, and for the pain she feels in her lower back. Although Inessa lives alone, following the death of her husband from a heart attack 5 years ago, she relies on a young man who lives in a small apartment attached to her house for help with activities of daily living and simply for company.

According to Inessa, the pain medication she was prescribed for her arthritis (short-acting hydrocodone/acetaminophen) is no longer working and she has come to you asking for either a different medication or a higher dose of the existing medication. Despite her reported pain, Inessa is ambulatory and appears cognitively intact. She takes a range of herbal supplements including St. John's wort, turmeric, and a "joint support" supplement, the ingredients of which she is unsure. She has a very insistent, demanding personality and is convinced she needs the new, or higher-dose, opioid medication.

1. **How would you respond to Inessa's request?**

2. **What alternatives to an opioid analgesic could you offer to Inessa?**

3. **If you end up prescribing an opioid analgesic for Inessa, would you require that she sign a patient-provider agreement? If so, what specific caveats would you include in the agreement?**

4. **Would it be prudent to include the young man who cares for her in discussions about treatment?**

Table 4: Example of functional goals and evidence used to assess progress[104]

Functional Goal	Evidence
Begin physical therapy	Letter from physical therapist
Sleeping in bed as opposed to lounge chair	Report by family member or friend (either in-person or in writing)*
Participation in pain support group	Letter from group leader
Increased activities of daily living	Report by family member or friend
Walk around the block	Pedometer recordings or written log of activity
Increased social activities	Report by family member or friend
Resumed sexual relations	Report by partner
Returned to work	Pay stubs from employer or letter confirming the patient is off of disability leave
Daily exercise	Gym attendance records or report from family member or friend

* Involving other persons requires explicit permission from the patient, and this permission should be documented.

Other ways to objectively monitor opioid use are checking prescription drug monitoring programs, completing urine drug tests/oral fluid tests, or random pill counts.

Relatively infrequent urine monitoring may be appropriate for low-risk patients on a stable dose of opioids (i.e., 1-2 times a year). More frequent or intense monitoring is appropriate for patients during the initiation of therapy or if the dose, formulation, or opioid medication is changed. Patients who may need more frequent or intense monitoring (i.e., 4-6 times a year) include:[104]

- Those with a prior history of an addictive disorder, past abuse, or other aberrant use
- Those in an occupation demanding mental acuity
- Older adults
- Patients with an unstable or dysfunctional social environment
- Those with comorbid psychiatric or medical conditions

It is important to recognize that urine drug testing is expensive and not all insurance companies will pay for frequent testing. Discuss the cost of testing with patients. Also, only order the test that is necessary. It is not necessary to order quantitative (definitive test) testing on all patients as this test can be very expensive. For low-risk patients urine drug screening (presumptive test), even done as a point of care test, may be sufficient. However, if the urine drug screen will not detect the drug of interest, then a quantitative test will be needed.

Trust is a necessary part of any patient/clinician relationship, but studies suggest that in the context of controlled substances, it is unwise to rely on a patient's word that medications are being consumed as prescribed. Although the use of more objective ways to monitor adherence to medication regimens is an imperfect science, such methods remain an essential component of periodic review. Multiple objective methods to assess adherence exist, but there is no single "best" approach and all such methods have both advantages and potential drawbacks.

In the context of family practice settings (and even pain specialist settings) unobserved urine collection is usually an acceptable procedure for drug testing. Prescribers, however, should be aware of the many ways in which urine specimens can be adulterated. Specimens should be shaken to determine if soap products have been added, for example. The urine color should be noted on any documentation that accompanies the specimen for evaluation, since unusually colored urine could indicate adulteration. Urine temperature and pH should be measured immediately after collection when possible.[131]

Prescribers should be familiar with the metabolites associated with each opioid that may be detected in urine, since the appearance of a metabolite can be misleading. A patient prescribed codeine, for example, may test positive for morphine because morphine is a metabolite of codeine. Similar misunderstandings may occur for patients prescribed hydrocodone who appear positive for hydromorphone or oxycodone and oxymorphone.

Opioid rotation and equianalgesic dosing

"Opioid rotation" means switching from one opioid to another in order to better balance analgesia and side effects. Rotation may be needed because of a lack of efficacy (often related to tolerance), bothersome or unacceptable side effects, increased dosing that exceeds the recommended limits of the current opioid (e.g., dose limitations of co-compounded acetaminophen), or inability to absorb the medication in its present form (i.e., if there is a change in the patient's ability to swallow, switch to a formulation that can be absorbed by a different route such as transdermal.)

Because of the large number of variables involved in how any given opioid will affect any given patient, opioid rotation must be approached cautiously, particularly when converting from an immediate-release formulation to an ER/LA product. As noted previously, equianalgesic charts must be used carefully, and titration must be done carefully and with appropriate monitoring. In some cases, because of the risk of potential harm during the time of rotating from one chronic opioid regimen to another, it may be wise to initially use lower doses of an ER/LA opioid than might be suggested by equianalgesic charts, while temporarily liberalizing, as needed, the use of a short-acting opioid.[138] This would then be followed by gradual titration of the LA opioid to the point where the as-needed short-acting opioid is incrementally reduced, until no longer necessary.

Equianalgesic dosing charts help clinicians determine the appropriate starting dose of an opioid when changing routes of administration or when changing from one opioid drug to another. Such charts must be used carefully, however. A high degree of variation has been found across the various charts and online calculator tools, and may account for some overdoses and fatalities.[132] The optimal dose for a specific patient must be determined by careful titration and appropriate monitoring, and clinicians must be mindful that patients may exhibit incomplete cross-tolerance to different types of opioids because of differences in the receptors or receptor sub-types to which different opioids bind.[138] In addition, the patient's existing level of opioid tolerance as well as concurrent medications that depress the central nervous system must be taken into account. Printed equianalgesic charts are common, and online calculators are also freely available (a common one can be accessed at clincalc.com/Opioids). Always work with a clinical pharmacist if you do not have a lot of experience with opioid rotation as this can be a risk factor for unintentional opioid overdose.

Recognizing patients with opioid use disorder

Whenever a clinician considers treating pain with a controlled substance, such as an opioid, risk of misuse or diversion is always a possibility, no matter how remote, and must be assessed. Some patient characteristics are predictive of a potential for drug abuse, misuse, or other aberrant behaviors. The factor that appears to be most strongly predictive in this regard is a personal or family history of alcohol or drug abuse.[28] Some studies have also shown that younger age and the presence of psychiatric conditions are also associated with aberrant drug-related behaviors.[28]

In evaluating patients with chronic pain for risk of addiction or signs that they may be abusing a controlled substance, it may be helpful to consider the sets of characteristics listed in Table 5.

Signs of physical dependence include the appearance of an abstinence syndrome with abrupt cessation or diminution of chronic drug administration and is not the same as OUD, a condition where patients lose control of their opioid use or compulsively use opioids. The nature and time of onset of this syndrome vary with drug actions and half-life. Slow tapering of the drug (e.g., 10-15% reduction in dosage per day or every other day) usually avoids the appearance of an abstinence syndrome.

Managing Non-Adherent Patients

Patients who exhibit aberrant drug-related behaviors or non-adherence to an opioid prescription should be monitored more closely than compliant patients. Concern that a patient is non-adherent should prompt a thorough evaluation.
The way clinicians interact with patients can affect the relationship (for better or worse) and influence treatment outcomes. A clinician's negative reactions to non-adherence might include anger at the patient, disappointment and sadness at the apparent betrayal of trust, or fear that the patient's behavior could expose the provider to legal jeopardy.[104]

The use of patient–provider agreements and/or informed consent documents can help clinicians navigate the uncertainties that can arise in cases of real or apparent non-adherence, and may help make the process less confrontational. Consultation with an addiction medicine specialist or psychiatrist may be necessary if addiction is suspected or if a patient's behavior becomes so problematic that it jeopardizes the clinician/patient relationship.

Table 5: Chronic pain patients vs. patients with an OUD[137]	
Patient with chronic pain	**Patient with an opioid use disorder**
Medication use is not out of control	Medication use is out of control
Medication use improves quality of life	Medication use impairs quality of life
Wants to decrease medication if adverse effects develop	Medication use continues or increases despite adverse effects
Is concerned about the physical problem being treated with the drug	Unaware of or in denial about any problems that develop as a result of drug treatment
Follows the practitioner-patient agreement for use of the opioid	Does not follow opioid agreement
May have left over medication	Does not have leftover medication
	Loses prescriptions
	Always has a story about why more drug is needed

Treatment Termination

Reasons for discontinuing an opioid analgesic can include the healing of or recovery from an injury, medical procedure, or condition; intolerable side effects; lack of response; or discovery of misuse of medications. Regardless of the reason, termination should be accomplished so as to minimize unpleasant withdrawal symptoms by tapering the opioid medication slowly, by carefully changing to a new formulation, or by effectively treating an opioid use disorder if it has developed. Approaches to weaning range from a slow 10% reduction per week to a more aggressive 25 to 50% reduction every few days.[28] In general, a slower taper will produce fewer unpleasant symptoms of withdrawal; however, this may not be the safe course of action for a patient experiencing side effects or who has OUD.

Opioid therapy must be discontinued or re-evaluated whenever the risk of therapy is deemed to outweigh the benefits being provided.

A clinician may choose to continue opioid treatment with intensified monitoring, counseling, and careful documentation if it is deemed in the best interest of the patient. This requires, however, careful consideration and a well-documented risk management plan that addresses the greater resources necessary for opioid continuation following evidence of misuse.

If termination of the physician/patient relationship is deemed necessary (though it rarely is), clinicians must ensure that the patient is transferred to the care of another physician or provider and ensure that the patient has adequate medications to avoid unnecessary risk, such as from uncontrolled or unpleasant withdrawal. Practitioners can be held accountable for patient abandonment if medical care is discontinued without justification or adequate provision for subsequent care.

Caution with dose escalation

When escalating opioid doses, be aware of two possible critical daily thresholds—50 and 90 MMED.[34] According to the CDC, doses >50 MMED are associated with more than double the risk of overdose compared to patients on <50 MMED.[31] For patients on >90 MMED, a 9-fold increase in mortality risk was observed compared with the lowest opioid doses. Ninety MMED is considered by several guidelines as a "red flag" dose beyond which careful assessment, more frequent monitoring, and documentation of expected benefits are required (note, however, that this limit doesn't apply to patients with severe cancer pain or end-of-life pain). The total MMED for all prescribed opioids should be used (MMED is automatically calculated on many state PDMP reports). Physician clinical judgment is also important in determining daily thresholds and the CDC limits can be used as a guide.

Role of ER/LA opioids and methadone

ER/LA opioids include methadone, transdermal fentanyl, and extended-release versions of opioids such as oxycodone, oxymorphone, hydrocodone, and morphine. A 2015 study found a higher risk for overdose among patients initiating treatment with ER/LA opioids than among those initiating treatment with immediate-release opioids.[124] As noted above, continuous, time-scheduled use of ER/LA opioids is not more effective or safer than intermittent use of immediate-release opioids, and ER/ LA opioids increase risks for opioid misuse or addiction.[31]

The 2016 CDC guidelines suggest that ER/LA opioids should be reserved for severe, continuous pain and should be considered only for patients who have received immediate-release opioids daily for at least 1 week.[31] Additional caution is required when prescribing ER/LA opioids in older adults or patients with renal or hepatic dysfunction because decreased clearance of drugs among these patients can lead to accumulation of drugs to toxic levels and persistence in the body for longer durations.

When an ER/LA opioid is prescribed in the primary care setting, using an agent with predictable pharmacokinetics and pharmacodynamics is preferred to minimize unintentional overdose risk (i.e., the unusual characteristics of methadone and transdermal fentanyl make safe prescribing of these medications for pain more challenging).[31]

The use of methadone for chronic pain in primary care should generally be avoided because of higher methadone-related risks for QTc prolongation and fatal arrhythmias.[31]

Equianalgesic dose ratios are highly variable with methadone, making conversion from other opioids difficult, with attendant increased risk of overdose. While methadone-related death rates decreased 9% from 2014 to 2015 overall, the rate increased in people ≥65 years of age.[139] If methadone or transdermal fentanyl is considered, refer patients to pain management specialists with expertise in using this medication.

BEFORE MOVING ONTO THE NEXT SECTION, PLEASE COMPLETE CASE STUDY 5 ON THE NEXT PAGE.

Protecting against opioid-induced adverse events

Prophylaxis for constipation—the most common opioid-induced adverse event—has been facilitated by the approval of methylnaltrexone subcutaneous administration and naloxegol oral administration for patients with chronic non-cancer pain. Other, less expensive medications like senna and docusate, are also effective to guard against constipation.

Both male and female patients on long-term opioid therapy are at risk for hypogonadism, thus current guidelines suggest that the endocrine function of all patients should be assessed at the start of long-term opioid therapy and at least annually thereafter.

Naloxone for opioid overdose

Naloxone (e.g., Narcan) is an opioid antagonist that quickly reverses the effects of opioid overdose. Naloxone is increasingly available to first responders, patients, and friends and family members of those prescribed opioids, and a generic formulation of nasal-spray naloxone was approved by the FDA in April, 2019.[141]

Case Study 5

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

Jeremiah has been your patient since he was a young boy. Now 33 years old, you have seen Jeremiah grow up into a physically strong, but emotionally vulnerable young man. Jeremiah struggled in school and chose to enter a training program for masons rather than pursue college. A self-described "partyer" who reports regular use of alcohol and cannabis, Jeremiah nonetheless has not reported any impacts of his substance use on his personal or work life. He has, in fact, been successful in both, earning a good living as a mason and supporting his wife and two sons.

But Jeremiah is currently on workman's compensation to recover from a compound fracture of his left foot and ankle sustained when a large section of a chimney he was working on collapsed and fell. He also tore the rotator cuff in his right shoulder when he fell backwards against the scaffolding poles during the accident. Both injuries required surgical interventions and his recovery has been slow. Jeremiah was prescribed a short-acting opioid after each surgery, which he has continued to use.

He has been regularly attending physical therapy sessions to restore strength in his left leg and to increase the range of motion in his right shoulder, but he complains that the therapy sessions are painful and that he doesn't think they're helping. He says his boss suggested that a long-acting opioid would be easier to use and would provide him more steady pain relief.

1. **How would Jeremiah's substance use affect your decision-making process related to his request for an ER/LA medication?**

2. **What steps might you take before agreeing to a trial of an ER/LA medication for Jeremiah?**

3. **What specific kind/dose of ER/LA medication might be most appropriate for Jeremiah if no contraindications were found in the pain and substance abuse assessment?**

4. **Name three specific functional goals that might be used as the basis for a pain management agreement with Jeremiah.**

Primary care providers should prescribe naloxone to patients at risk of overdose, including those:

- With renal or hepatic dysfunction
- Taking opioid doses >50 MMED
- Co-prescribed benzodiazepines or other sedating medications
- With a history of overdose or OUD
- Starting treatment for opioid use disorder

Many states allow patients, family members, caregivers, and/or friends to request naloxone from their local pharmacist. Anyone receiving naloxone should be taught how to use the device and about the common signs of overdose (slow or shallow breathing, gasping for air, unusual snoring, pale or bluish skin, not waking up or responding, pin point pupils, slow heart rate).

A variety of naloxone products are available. The intranasal device with atomizer and intramuscular (IM) shots require the most manipulation in order to administer. Intranasal naloxone and the auto-IM injector are easier to use, but vary greatly in terms of price and insurance coverage.

Successful opioid tapering

Patients who do not achieve functional goals on stable or increasing opioid doses or those with unacceptable side effects, should have the opioid tapered or discontinued. Patients sometimes resist tapering or discontinuation, fearing increased pain. However, a 2017 systematic review found that dose reduction or discontinuation resulted in reduced pain (eight studies), improved function (five studies) and improved quality of life (three studies), although the evidence was not strong because the analysis included poor-quality studies with uncontrolled designs and the interventions and outcome measures were heterogeneous.[142]

Recommendations for tapering schedules vary. One source recommends a 10% decrease weekly based on years of opioid use (i.e., 10% decrease monthly for patients using opioids ≥4 years). For patients on high-dose opioids (i.e., ≥90 MMED), taper 10% until patient is taking 30% of the total initial dose, then recalculate 10% taper based on the new total opioid dose to slow taper.[143] The rate of opioid taper should be adjusted based on patient-specific factors such as the severity of withdrawal symptoms.

Table 6: Recommendations for preventing or treating opioid-induced side effects[140]	
Constipation	Methylnaltrexone or naloxegol Prophylactic mild peristaltic stimulant (e.g. bisacodyl or senna) If no bowel movement for 48 hours, increase dose of bowel stimulant If no bowel movement for 72 hours, perform rectal exam If not impacted, provide additional therapy (suppository, enema, magnesium citrate, etc.)
Nausea or vomiting	Consider prophylactic antiemetic therapy Add or increase non-opioid pain control agents (e.g. acetaminophen) If analgesia is satisfactory, decrease dose by 25% Treat based on cause
Sedation	Determine whether sedation is due to the opioid – if so, lower opioid dose immediately Eliminate nonessential CNS depressants (such as benzodiazepines) Reduce dose by 20-30% Add or increase non-opioid or non-sedating adjuvant for additional pain relief (such as NSAID or acetaminophen)so the opioid can be reduced Change opioid Prescribe naloxone
Pruritus	Consider treatment with antihistamines Change opioid
Hallucination or dysphoria	Evaluate underlying cause Eliminate nonessential CNS acting medications
Sexual dysfunction	Reduce dose Testosterone replacement therapy may be helpful (for men) Erection-enhancing medications (e.g., sildenafil)

In 2019 the FDA, recognizing the risks associated with abrupt discontinuation of opioid analgesics, required new labeling for opioid analgesics to guide prescribers about safe tapering practices.[138]

The key elements include:[144]

- Do not abruptly discontinue opioid analgesics in patients physically dependent on opioids. Counsel patients not to discontinue their opioids without first discussing the need for a gradual tapering regimen.
- Abrupt or inappropriately rapid discontinuation of opioids is associated with serious withdrawal symptoms, uncontrolled pain, and suicide.
- Ensure ongoing care of the patient and mutually agree on an appropriate tapering schedule and follow-up plan.
- In general, taper by an increment of no more than 10-20% every 2-4 weeks.
- Pause taper if the patient experiences significantly increased pain or serious withdrawal symptoms.
- Use a multimodal approach to pain management, including mental health support (if needed).
- Reassess the patient regularly to manage pain and withdrawal symptoms that emerge and assess for suicidality or mood changes.
- Refer patients with complex comorbidities or substance use disorders to a specialist.

Opioid use disorder (OUD)

OUD is a problematic pattern of opioid use that causes significant impairment or distress.[145] As with other chronic diseases, OUD usually involves cycles of relapse and remission. DSM-5 diagnosis of OUD is based on clinical evaluation and determination that a patient has problematic opioid use leading to clinically significant impairment or distress involving at least two of the following within a 12-month period:[145]

- Opioids taken in larger amounts, or for longer periods, than intended
- Persistent desire or unsuccessful attempts to control or reduce use
- Significant time lost obtaining, consuming, and recovering from opioids
- Craving or a strong desire or urge to use opioids
- Failure to complete obligations (i.e., work, home, or school) due to opioids
- Persistent or recurrent social or interpersonal problems due to opioids
- Giving up enjoyable social, work, or recreational activities due to opioids
- Recurrent opioid use in situations in which it is physically hazardous (e.g., driving)
- Continued use despite a physical or psychological problem caused by or worsened by opioid use
- Tolerance (unless opioids are being taken as prescribed)
- Using opioids to prevent withdrawal symptoms (unless opioids are being taken as prescribed)

OUD is not a binary diagnosis, rather it exists as a continuum, with DSM-5 describing 3 levels of severity:

- Mild OUD (2-3 criteria)
- Moderate OUD (4-5 criteria)
- Severe OUD (≥ 6 criteria)

More than 2 million Americans have OUD, and the number is growing.[70] OUD can be effectively managed with medication-assisted treatment (MAT), but only an estimated 20% of adults with OUD currently receive such treatment.[146]

Medications to treat OUD

The FDA has approved three medications for treating OUD: buprenorphine, methadone, and extended-release naltrexone (Table 7). Buprenorphine and methadone can reduce opioid cravings and all three can prevent misuse.[141] Each medication has a unique mechanism of action and involve different formulations, methods of induction and maintenance, patterns of administration, and regulatory requirements.

Methadone

Methadone is a synthetic, long-acting opioid agonist that fully activates mu-opioid receptors in the brain.[148] This activity reduces the unpleasant/dysphoric symptoms of opioid withdrawal, and, at therapeutic doses, it blunts the "highs" of shorter-acting opioids such as heroin, codeine, and oxycodone. Patients do not have to experience opioid withdrawal before starting methadone.

Table 7. FDA-approved medications for OUD[147]
Buprenorphine • Buprenorphine/naloxone buccal film (Bunavail) • Buprenorphine/naloxone sublingual film (Suboxone, generics) • Buprenorphine/naloxone sublingual tablets (Zubsolv, generics) • Buprenorphine sublingual tablets (generics) • Buprenorphine subdermal implant (Probuphine) • Buprenorphine extended-release subcutaneous injection (Sublocade)
Methadone • Tablets (Dolophine, MethaDose, generics) • Oral concentrate (MethaDose, generics)
Naltrexone extended-release injection (Vivitrol)

It may, however, take days to weeks to achieve a therapeutic dose, which requires individualized monitoring in order to minimize cravings and reduce the risk of relapse.

As a full agonist, methadone sustains opioid tolerance and physical dependence, thus missing doses may precipitate opioid withdrawal. Overdose risk is highest in the first two weeks of methadone treatment,[149] after which risk is significantly lower compared to people who are not in treatment.[150,151]

Common side effects of methadone are constipation, vomiting, sweating, dizziness, and sedation. Although respiratory depression can be induced by methadone, the FDA advises that methadone not be withheld from patients taking benzodiazepines or other central nervous system depressants because the risk of overdose is even higher among patients not on methadone for OUD.[152] The other potential harms of methadone include hypogonadism, which is a potential side effect of chronic use of any opioid, and QTc segment prolongation.

Buprenorphine

Buprenorphine is a high-affinity partial opioid agonist at the mu-opioid receptor as well as an antagonist of the kappa opioid receptor.[153] Like methadone, buprenorphine can relieve opioid withdrawal symptoms, and, because of its partial agonist effect, it can reduce the rewarding effect of other opioids used simultaneous with buprenorphine. Buprenorphine's partial agonist status also translates into a lower risk of respiratory depression compared to methadone and other opioids,[148] and a therapeutic dose may be achieved within a few days.[155]

Buprenorphine is available as sublingual tablets, sublingual/buccal films, subdermal implants, or extended-release subcutaneous injection (Table 10). Some film and tablet formulations are combined with the opioid antagonist naloxone to discourage misuse by crushing and injecting the medication. (A buprenorphine-only patch [Butrans] is only FDA-approved as an analgesic.)

Some forms of buprenorphine can be self-administered by patients after filling their prescription at regular pharmacies.

In order to prescribe buprenorphine, physicians in the United States must complete an 8-hour training and apply for a waiver (informally called an X-waiver) from the Drug Enforcement Administration (for details see "Obtaining an X-waiver" section below). The Comprehensive Addiction and Recovery Act of 2016 authorized nurse practitioners and physician assistants to be eligible to apply for training and X-waivers, although the associated required training is 24 hours.[156]

As with methadone, buprenorphine sustains opioid tolerance and physical dependence in patients, so discontinuation can lead to withdrawal—although buprenorphine's withdrawal syndrome may be less severe. The most common side effects are constipation, vomiting, headache, sweating, insomnia, and blurred vision. One risk of buprenorphine (as well as naltrexone) is the risk of precipitating opioid withdrawal at first dose if the patient has recently used either prescription or illicit drugs, due to buprenorphine's partial-agonist properties high binding affinity for the opioid receptor.[141] Thus, a patient must be in mild to moderate withdrawal prior to initiation to avoid precipitating withdrawal. The risk of opioid overdose declines immediately when patients with OUD initiate buprenorphine treatment.[145] The risk of hypogonadism is lower with buprenorphine compared to methadone, and buprenorphine is not associated with QTc prolongation or cardiac arrhythmias.[157]

The various non-oral routes of buprenorphine avoid the significant hepatic metabolism inherent with oral administration, and appear to be largely equivalent in their efficacy for maintaining abstinence and reducing risk of overdose. For example, a randomized trial comparing buprenorphine implant to sublingual buprenorphine found higher levels of negative urine screens and abstinence with the implant, but the differences did not reach statistical significance.[158] (Note that use of implantable agents require stabilization on sublingual doses first.)

"Buprenorphine treatment provides one of the rare opportunities in primary care to see dramatic clinical improvement: it's hard to imagine a more satisfying clinical experience than helping a patient escape the cycle of active addiction."

--Wakeman et al. NEJM 2018;379(1):1-4

Extended-release naltrexone

Naltrexone is not an opioid. It is a full antagonist of the mu-opioid receptor, which blocks both the euphoric and analgesic effects of all opioids, including endogenous opioids (i.e., endorphins) and also reduces cravings for opioids.[153] Naltrexone does not cause physical dependence, nor does it produce any of the rewarding effects of opioids. Patients may try to use opioids while on extended-release naltrexone, but it is unlikely that they will experience any rewarding effects from such use, unless the binding affinity of naltrexone is overcome.[147] The most common side effects of extended-release naltrexone are injection site pain, nasopharyngitis, insomnia, and toothache.

Treatment initiation requires a 7-10 day period during which the patient is free from all opioids, including methadone and buprenorphine. This is usually achieved with medicallysupervised withdrawal followed by at least 4 to 7 days without any opioids (including methadone and buprenorphine). This process is a very significant barrier to naltrexone use.[147]

Naltrexone is currently available both as a once-daily oral tablet and in a once monthly, extended-release depot injection. The oral formulation, however, was found to be no better than placebo in a 2011 Cochrane review of 13 trials with 1,158 participants,[159] and only the extended-release formulation has been approved for OUD by the FDA. Patients may have an increased risk of overdose when they approach the end of the 28-day period of the extended-release formulation.[160]

Naloxone vs. Naltrexone: What's the difference?

Naloxone (Narcan) is an opioid antagonist given by injection or nasal spray to reverse overdoses. It acts within minutes and lasts for only about an hour due to rapid metabolism.

Naltrexone has a very similar chemical structure to Naloxone and is also an opioid antagonist, but it acts more slowly and lasts longer. Extended-release naltrexone is used clinically to block cravings for opioids and other drugs.

Does MAT really work?

Abundant evidence from decades of randomized trials, clinical studies, and meta-analyses suggests that agonist or partial-agonist opioid treatment used for an indefinite period of time is the safest option for treating OUD.[147, 155] (The evidence base for extended-release naltrexone is much less robust.)[147]

A small randomized trial and a large cohort study demonstrated that people with OUD treated with methadone or buprenorphine are less likely to die, less likely to overdose, and more likely to remain in treatment. [153,161] MAT is also associated with lower risks for HIV and other infections, and improved social functioning and quality of life compared to people not on MAT.[30]

Data suggest that MAT is more effective than psychotherapeutic interventions alone, and is just as effective whether psychotherapeutic interventions are used concurrently with medication treatment or not. For example, data from Massachusetts Medicaid beneficiary claims between 2004 and 2010 show significantly lower relapse rates with both buprenorphine and methadone compared to a behavioral health intervention alone.[162]

Although the evidence base for intramuscular naltrexone is less robust than for methadone or buprenorphine, it has been shown to significantly decrease opioid misuse in patients with mild-to-moderate OUD.[147] For example, one trial randomized 250 patients with OUD who completed inpatient detoxification (≥ 7 days off all opioids) to 24 weeks of naltrexone intramuscular injection (380 mg/month) vs. placebo.[163] At follow-up, 90% in the naltrexone group were abstinent compared to 35% in the placebo group.

Psychosocial treatments

Psychosocial and/or behavioral interventions can be used in combination with medications in order to treat the "whole patient" (e.g., comorbid psychiatric symptoms, social support needs). The National Academy of Sciences, however, notes that psychosocial services may not be available to all patients and recommends that the lack of such supports should not be a barrier to using MAT.[147]

For example, a 2012 trial randomized 230 adults with OUD to one of three groups: methadone without extra counseling vs. methadone with standard counseling vs. methadone with counseling in the context of smaller caseloads.[164] At one-year follow-up there were no significant differences between the groups in rates of retention in treatment or urine tests positive for opioids. Three other randomized trials comparing buprenorphine with medical management alone vs. buprenorphine plus cognitive behavioral therapy or extra counseling sessions also found no significant differences in key opioid-related outcomes.[165-167]

Nonetheless, psychosocial, behavioral, and peer-support interventions may have many profoundly important benefits for patients beyond strictly opioid-related outcomes, such as improving self-confidence, self-advocacy, general quality of life, and improvements in legal, interpersonal, and occupational functioning.[141] Some guidelines and authors advocate for the use of psychosocial interventions, but suggest that the lack of such interventions at a given place or time should not be a barrier to the use of MAT.[147,169]

Tapering protocols

OUD guidelines do not recommend a duration of MAT treatment, which could be for an indefinite period of time because of the high risk of relapse with discontinuation.[147] For example, a population-based retrospective study of 14,602 patients who discontinued methadone treatment found that only 13% had successful outcomes (no treatment re-entry, death, or opioid-related hospitalization) within 18 months of taper.[169]

Nonetheless, some patients may want to stop opioid agonist therapy. An ideal time frame for a trial of MAT tapering has not been established. Tapering should always be at the patient's discretion, and all decisions should be based on a thorough dialogue between patient and provider. Goals should be framed functionally, for example maintaining employment, avoiding using illicit opioids or other drugs, continuing with social/emotional support programs, etc.

Misconceptions about OUD Treatment

Stigma and misunderstanding surround the issues of addiction in general and OUD in particular.[147] These include counterproductive ideologies that portray addiction as a failure of will or a moral weakness, as opposed to understanding OUD as a chronic disease of the brain requiring medical management, which is no different, in principle, from the approach used to manage other chronic diseases such as diabetes or hypothyroidism. Some stigma and misunderstanding may arise from a lack of awareness of how treatment of OUD has evolved in the past 15 years.[170] Table 8 summarizes some common misconceptions about OUD treatment.

Addressing stigma

High levels of stigma persist among some medical professionals and recovery communities toward people with OUD and medications used to treat OUD.[147] A 2016 national opinion survey (n=264) found that 54% of respondents thought people addicted to opioid pain relievers were to blame for their addiction, 46% felt such people are irresponsible, and 45% said they would be unwilling to work closely with such people.[162]

A 2014 survey of 1,010 primary care physicians found similar, or even higher, levels of stigma related to people with OUD.[167] Interviews with patients using methadone for OUD confirm that this group experiences high rates of stigma and discrimination related to their medication use in interactions with the public and with health care professionals,[174] which erodes their psychological well-being and may inhibit them from entering treatment.[147]

Table 8. Misconceptions vs. realities of OUD treatment[171]

Misconceptions	Reality
Buprenorphine treatment is more dangerous than other chronic disease management.	Buprenorphine treatment is less risky than many other routine treatments, such as titrating insulin or starting anticoagulation and easier to administer. It is also safer than prescribing many opioids (e.g., oxycodone, morphine).
Using methadone or buprenorphine is simply a "replacement" addiction.	Addiction is compulsive use of a drug despite harm. When taken as prescribed, methadone and buprenorphine improve function, autonomy, and quality of life and patients using these drugs do not meet the definition of addiction.
Detoxification for OUD is effective.	No data show that detoxification programs are effective for OUD, and, in fact, such interventions may increase the risk of overdose death by eliminating tolerance.
Prescribing buprenorphine is time consuming and burdensome.	Buprenorphine treatment can be readily managed in a primary care setting, and in-office induction or intensive behavioral therapy are not required for effective treatment.

Health care professionals can combat stigma by examining their own attitudes and beliefs and by consciously and consistently using neutral, "person-first," and non-stigmatizing language such as "being in recovery" instead of "being clean" or "person with opioid use disorder" rather than "addict," "user," or "drug abuser."[175]

Pregnancy and OUD

Pregnant women with untreated OUD have up to six times more maternal complications than women without OUD, including low birth weight and fetal distress, while neonatal complications among babies born to mothers with OUD range from neonatal abstinence syndrome and neurobehavioral problems to a 74-fold increase in sudden infant death syndrome.[177]

Both methadone and buprenorphine are recommended for treating OUD in pregnancy to improve outcomes for both mother and newborn.[141] The efficacy and safety of methadone treatment for OUD in pregnant women was established in the 1980s, showing that maternal and neonatal outcomes in women on methadone treatment during pregnancy are similar to women and infants not exposed to methadone.[177] More recent research suggests that buprenorphine treatment has similar, or superior, benefits in this population.[178]

The safety of extended-release naltrexone has not yet been established for pregnant women, and naltrexone is currently not recommended for the treatment of OUD in pregnant women.[147]

Despite this solid evidence base, most pregnant women with OUD do not receive any treatment with medications.[179] Among women who do receive treatment during pregnancy, many fall out of treatment during the post-partum period due to gaps in insurance coverage and other systemic barriers. An integrated approach with close collaboration between OUD treatment providers and prenatal providers has been described as the "gold standard" for care, and further research is needed to investigate interventions that could help to increase treatment retention.[147]

Treating acute pain in patients on MAT

Some physicians may not prescribe effective opioid analgesia for patients with OUD on MAT due to concerns about respiratory depression, overdose, or drug diversion. As a result, this population is at particular risk of under-treatment for acute pain.

Physicians may also mistakenly assume that acute pain is adequately controlled with the long-term opioid agonist (i.e., methadone) or partial agonist (i.e., buprenorphine). Although potent analgesics, methadone and buprenorphine have an analgesic duration of action (four to eight hours) that is substantially shorter than their suppression of opioid withdrawal (24 to 48 hours).[180]

Non-opioid analgesics (e.g., acetaminophen and NSAIDs) are first-line options for treating acute pain in this population. For moderate-to-severe pain not adequately controlled with non-opioids, however, judicious use of opioid analgesics should be considered. Patients on MAT generally have a high cross-tolerance for analgesia, leading to shorter durations of analgesic effects. Higher opioid doses administered at shorter intervals may thus be necessary. Concomitant opioids can be given for pain to a patient prescribed buprenorphine, but typically hydromorphone or fentanyl may be the most effective due to competitive binding at the opioid receptor.

Since extended-release naltrexone will block the effects of any opioid analgesics, acute pain in such patients (e.g., that associated with dental work, surgery, or traumatic injury) should be treated with regional analgesia, conscious sedation, non-opioid analgesics, or general anesthesia.[30]

Palliative Care

Palliative care is specialized medical care for people with serious illness focused on relieving symptoms and improving quality of life for both the patient and the family. Palliative care involves three key areas: symptom management (e.g., pain, nausea, constipation), supporting patients and their loved ones as they cope with illness and death, and communication and education about the illness through advance care planning (ACP).[181] The field of palliative care emerged from a hospice tradition but in the past decade a more nuanced model of care has been introduced, which integrates palliative care with disease-modifying care across the duration of an illness and includes consideration of those affected by the death of the individual.

Pain control is a central focus of palliative care, but the goal of pain management is not simply the elimination of all pain, it is the control of pain sufficient for a given patient to achieve his or her highest quality of life in the moment.[182] In the palliative care setting, clinicians may need to manage acute pain (e.g., post-surgical or post-treatment pain) or chronic pain or both types of pain simultaneously.

Clinicians can avail themselves of a wide range of pharmacologic and non-pharmacologic approaches for pain management, which should be employed using the following general principles:

- Identify and treat the source of the pain, if possible, although pain treatment can begin before the source of the pain is determined
- Select the simplest approach first. This generally means using non-pharmacologic approaches as much as possible and/or trying medications with the least severe potential side effects, and at the lowest effective doses
- Establish a function-based management plan if treatment is expected to be long-term

A range of non-pharmacological treatments may help patients manage chronic pain, which can be used alone or in combination with pharmacological treatments:

- Physical therapy
- Yoga
- Acupuncture
- Massage
- Transcutaneous electrical nerve stimulation
- Cognitive behavioral therapy
- Mindfulness meditation
- Weight loss

Medications used to treat chronic pain in palliative settings include:

- acetaminophen
- non-steroidal anti-inflammatory drugs (NSAIDs)
- antidepressants
- anticonvulsants
- topical lidocaine or capsaicin
- cannabinoid-based therapies
- opioids

Opioids are classified by the Drug Enforcement Agency according to their presumed abuse and addiction potential, although the evidence base for making these differentiations continues to evolve. Tramadol, for example, is now known to have as much potential for abuse as opioids in more restrictive classes.[171]

Managing end-of-life pain

Although pain relief is often considered—and may sometimes be—an end unto itself, pain management and control of symptoms at the end of life may be more appropriately viewed as means of achieving the more primary goal of improving or maintaining a patient's overall quality of life. For some patients, mental alertness sufficient to allow maximal interactions with loved ones may be more important than physical comfort. Optimal pain management, in such cases, may mean lower doses of an analgesic and the experience, by the patient, of higher levels of pain.

The end of life is often characterized by a reduced level of consciousness or complete lack of consciousness. This can make assessments of pain very challenging. If a patient is not alert enough to communicate, nonverbal signs or cues must be used to determine if the patient is experiencing pain and to what degree an analgesic approach is effective. Signs of discomfort that are accompanied by more rapid breathing or heart rate should be taken more seriously.

Opioids are often valuable for providing effective analgesia at the end of life, and opioid formulations are available in such variety in the U.S. that, typically, a pain regimen can be tailored to each patient. Because there is great between-patient variability in response to particular opioid agents no specific agent is superior to another as first-line therapy. Opioid-related side effects must be considered in advance of treatment and steps must be taken to minimize these effects to the extent possible, since adverse effects contribute significantly to analgesic nonadherence. This is particularly true for constipation and sedation.

A stimulant, such as methylphenidate or dextroamphetamine, might be added to offset sedative effects, typically starting at a dose of 5 to 10 mg once or twice daily. Other adverse effects, including respiratory depression, are greatly feared and may lead to clinician under-prescribing and reluctance by patients to take the medication, despite the rarity of this event in persons with cancer.[183] Despite this fear, studies have revealed no correlation between opioid dose, timing of opioid administration, and time of death.[184]

A wide range of complementary and alternative therapies (CAT) are commonly used in end-of-life care. CAT interventions are aimed at reducing pain, inducing relaxation, and enhancing a sense of control over the pain or the underlying disease. Breathing exercises, relaxation, imagery, hypnosis, and other behavioral therapies are among the modalities shown to be potentially helpful to patients.[185] Psychosocial interventions for end-of-life pain may include cancer pain education, hypnosis and imagery based methods, and coping skills training. Educational programs are one of the most common interventions to address cancer pain barriers, and current studies provide high-quality evidence that pain education is feasible, cost-effective, and practical in end-of-life settings.[186]

Conclusions

Managing pain is particularly challenging in an era when society is grappling with an epidemic of opioid misuse and overdose. This learning activity has reviewed an evidence-based path forward, based on a biopsychosocial model of pain, and an emphasis on holistic assessment, individualized treatment planning, and multi-modal therapeutic approaches.

Physicians and caregivers need to base pain treatment plans on realistic functional goals and the level of pain management needed to reach those goals using a shared decision-making approach. As detailed in this activity, chronic pain syndromes respond differently to available pharmacologic and non-pharmacologic treatments, but, in general, non-drug options (which can be as effective as drug options) should be tried first when possible. When drug options are considered, it is important to maximize non-opioid options before prescribing opioids. For selected patients requiring opioids, the risk of long-term opioid treatment should be minimized through patient education, screening of high-risk patients for OUD, continuous monitoring, use of alternative non-opioid options, and careful tapering when appropriate.

Since much acute pain is self-limiting and remits with healing (typically within a month), helping patients frame expectations about acute pain and pain relief can provide reassurance and reduce fear, worry, and distress. Multimodal approaches should be used to manage acute pain, combining non-drug (e.g. interventional procedures, physical rehabilitation, and psychological support) as well as appropriate drug-based options. Opioid analgesics should be reserved for severe pain that does not respond to all other approaches, and then should be used at the lowest doses, and shortest durations, appropriate for the pain intensity expected with the precipitating event.

This activity has laid out the evidence supporting these conclusions and provides the basis for improved treatment and reduced risk, both for patients and society at large.

References

1. Centers for Disease Control & Prevention. Prescription Painkiller Overdoses in the US. Vital Signs. 2011.
2. Centers for Disease Control & Prevention. Understanding the epidemic. https://www.cdc.gov/drugoverdose/epidemic/index.html. Published 2019. Accessed April 1 2019.
3. Centers for Disease Control & Prevention. Vital signs: overdoses of prescription opioid pain relievers---United States, 1999--2008. MMWR Morbidity and mortality weekly report. 2011;60(43):1487-1492.
4. Centers for Disease Control & Prevention. Increase in fatal drug overdoses across the United States driven by synthetic opioids before and during the COVID-19 pandemic. https://emergency.cdc.gov/han/2020/han00438.asp?ACSTrackingID=USCDC_511-DM44961&ACSTrackingLabel=HAN%20438%20-%20General%20Public&deliveryName=USCDC_511-DM44961. Accessed December 28, 2020.
5. Centers for Disease Control & Prevention. 12 Month-ending provisional number of drug overdose deaths. https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm. Accessed December 28, 2020.
6. Centers for Disease Control & Prevention. Opioid overdose: Understanding the Epidemic. https://www.cdc.gov/drugoverdose/images/3-waves-2019.PNG. Published 2021. Accessed June 10, 2021.
7. Banta-Green CJ, Merrill JO, Doyle SR, Boudreau DM, Calsyn DA. Opioid use behaviors, mental health and pain--development of a typology of chronic pain patients. Drug and alcohol dependence. 2009;104(1-2):34-42.
8. Boscarino JA, Rukstalis MR, Hoffman SN, et al. Prevalence of prescription opioid-use disorder among chronic pain patients: comparison of the DSM-5 vs. DSM-4 diagnostic criteria. Journal of addictive diseases. 2011;30(3):185-194.
9. Fleming MF, Balousek SL, Klessig CL, Mundt MP, Brown DD. Substance use disorders in a primary care sample receiving daily opioid therapy. J Pain. 2007;8(7):573-582.
10. Centers for Disease Control & Prevention. 2018 Annual Surveillance Report of Drug-Related Risks and Outcomes--United States Surveillance Special Report 2. August 31 2018.
11. Muhuri PK, Gfroerer JC, Davies MC. Associations of Nonmedical Pain Reliever Use and Initiation of Heroin Use in the United States. SAMHSA;August 2013.
12. Busse JW, Wang L, Kamaleldin M, et al. Opioids for Chronic Noncancer Pain: A Systematic Review and Meta-analysis. Jama. 2018;320(23):2448-2460.
13. Krebs EE, Gravely A, Nugent S, et al. Effect of Opioid vs Nonopioid Medications on Pain-Related Function in Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain: The SPACE Randomized Clinical Trial. Jama. 2018;319(9):872-882.
14. Arner S, Meyerson BA. Lack of analgesic effect of opioids on neuropathic and idiopathic forms of pain. Pain. 1988;33(1):11-23.
15. Covington EC. Anticonvulsants for neuropathic pain and detoxification. Cleveland Clinic journal of medicine. 1998;65 Suppl 1:SI21-29.
16. U.S. Department of Health and Human Services. Pain Management Best Practices Inter-Agency Task Force Report: Updates, Gaps, Inconsistencies, and Recommendations. https://www.hhs.gov/ash/advisory-committees/pain/reports/index.html. Published 2019. Accessed June 10 2019.
17. Wells N, Pasero C, McCaffery M. Improving the Quality of Care Through Pain Assessment and Management. In: Hughes RG, ed. Patient Safety and Quality: An Evidence-Based Handbook for Nurses. Rockville (MD)2008.
18. Goodwin J, Bajwa ZH. Understanding the patient with chronic pain. In Principles and Practice of Pain Medicine 2nd ed. New York, NY: McGraw-Hill Companies, Inc.; 2004.
19. Gordon DB, Dahl JL, Miaskowski C, et al. American pain society recommendations for improving the quality of acute and cancer pain management: American Pain Society Quality of Care Task Force. Archives of internal medicine. 2005;165(14):1574-1580.
20. Olsen MF, Bjerre E, Hansen MD, Tendal B, Hilden J, Hrobjartsson A. Minimum clinically important differences in chronic pain vary considerably by baseline pain and methodological factors: systematic review of empirical studies. J Clin Epidemiol. 2018;101:87-106 e102.
21. Keller S, Bann CM, Dodd SL, Schein J, Mendoza TR, Cleeland CS. Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. The Clinical journal of pain. 2004;20(5):309-318.
22. Krebs EE, Lorenz KA, Bair MJ, et al. Development and initial validation of the PEG, a three-item scale assessing pain intensity and interference. Journal of general internal medicine. 2009;24(6):733-738.
23. Krebs EE, Carey TS, Weinberger M. Accuracy of the pain numeric rating scale as a screening test in primary care. Journal of general internal medicine. 2007;22(10):1453-1458.
24. Bjoro K, Herr K. Assessment of pain in the nonverbal or cognitively impaired older adult. Clinics in geriatric medicine. 2008;24(2):237-262.
25. Schug SA, Bruce J. Risk stratification for the development of chronic postsurgical pain. Pain Rep. 2017;2(6):e627.
26. Traeger AC, Henschke N, Hubscher M, et al. Estimating the Risk of Chronic Pain: Development and Validation of a Prognostic Model (PICKUP) for Patients with Acute Low Back Pain. PLoS Med. 2016;13(5):e1002019.
27. Sipila R, Estlander AM, Tasmuth T, Kataja M, Kalso E. Development of a screening instrument for risk factors of persistent pain after breast cancer surgery. Br J Cancer. 2012;107(9):1459-1466.
28. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain. 2009;10(2):113-130.
29. Babor TF, McRee BG, Kassebaum PA, Grimaldi PL, Ahmed K, Bray J. Screening, Brief Intervention, and Referral to Treatment (SBIRT): toward a public health approach to the management of substance abuse. Subst Abus. 2007;28(3):7-30.
30. Substance Abuse and Mental Health Services Administration. Medications for Opioid Use Disorder Treatment Improvement Protocol 63. HHS Publication No SMA 18-5063FULLDOC. 2018.
31. Centers for Disease Control & Prevention. CDC guideline for prescribing opioids for chronic pain—United States, 2016. MMWR Recommendations and Reports. 2016;65(1):16.
32. Hauswirth B. Blunt calls for Missouri PDMP bill. https://www.missourinet.com/2019/04/17/blunt-calls-for-missouri-pdmp-bill-emphasizes-importance-of-broadband/. Published 2019. Accessed April 24 2019.
33. Federation of State Medical Boards. Prescription Drug Monitoring Programs State-by-state overview. http://www.fsmb.org/siteassets/advocacy/key-issues/prescription-drug-monitoring-programs-by-state.pdf. Published 2019. Accessed April 24 2019.
34. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain - United States, 2016. MMWR Recomm Rep. 2016;65(1):1-49.
35. Peppin JF, Passik SD, Couto JE, et al. Recommendations for urine drug monitoring as a component of opioid therapy in the treatment of chronic pain. Pain medicine. 2012;13(7):886-896.
36. Christo PJ, Manchikanti L, Ruan X, et al. Urine drug testing in chronic pain. Pain physician. 2011;14(2):123-143.
37. Food and Drug Administration. Opioid analgesic risk evaluation and mitigation strategy (REMS). https://www.fda.gov/drugs/information-drug-class/opioid-analgesic-risk-evaluation-and-mitigation-strategy-rems. Published 2018. Accessed June 10 2019.
38. Fransen M, McConnell S, Harmer AR, Van der Esch M, Simic M, Bennell KL. Exercise for osteoarthritis of the knee. The Cochrane database of systematic reviews. 2015;9(1).
39. Kang JW, Lee MS, Posadzki P, Ernst E. T'ai chi for the treatment of osteoarthritis: a systematic review and meta-analysis. BMJ Open. 2011;1(1):2010-000035.
40. Sherman KJ, Cherkin DC, Wellman RD, et al. A randomized trial comparing yoga, stretching, and a self-care book for chronic low back pain. Archives of internal medicine. 2011;171(22):2019-2026.
41. Messier SP, Mihalko SL, Legault C, et al. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: the IDEA randomized clinical trial. Jama. 2013;310(12):1263-1273.
42. Hinman RS, McCrory P, Pirotta M, et al. Acupuncture for chronic knee pain: a randomized clinical trial. Jama. 2014;312(13):1313-1322.
43. Perlman AI, Sabina A, Williams AL, Njike VY, Katz DL. Massage therapy for osteoarthritis of the knee: a randomized controlled trial. Archives of internal medicine. 2006;166(22):2533-2538.
44. Reid MC, Eccleston C, Pillemer K. Management of chronic pain in older adults. Bmj. 2015;13(350).
45. Morley S, Eccleston C, Williams A. Systematic review and meta-analysis of randomized controlled trials of cognitive behaviour therapy and behaviour therapy for chronic pain in adults, excluding headache. Pain. 1999;80(1-2):1-13.
46. Hilton L, Hempel S, Ewing BA, et al. Mindfulness Meditation for Chronic Pain: Systematic Review and Meta-analysis. Ann Behav Med. 2017;51(2):199-213.

47. American Geriatrics Society Panel on Pharmacological Management of Persistent Pain in Older Persons. Pharmacological management of persistent pain in older persons. J Am Geriatr Soc 2009;57:1331–46.
48. Lee WM. Acetaminophen (APAP) hepatotoxicity-Isn't it time for APAP to go away? J Hepatol. 2017;20(17):32148-32147.
49. Hawkey CJ, Svedberg LE, Naesdal J, Byrne C. Esomeprazole for the management of upper gastrointestinal symptoms in patients who require NSAIDs: a review of the NASA and SPACE double-blind, placebo-controlled studies. Clinical drug investigation. 2009;29(10):677-687.
50. Desai JC, Sanyal SM, Goo T, et al. Primary prevention of adverse gastroduodenal effects from short-term use of non-steroidal anti-inflammatory drugs by omeprazole 20 mg in healthy subjects: a randomized, double-blind, placebo-controlled study. Digestive diseases and sciences. 2008;53(8):2059-2065.
51. Food and Drug Administration. FDA Briefing Document: Joint meeting of the arthritis advisory committee and the drug safety and risk management advisory committe April 24 and 25 2018. 2018.
52. Brown T. CV safety of celecoxib similar to naproxen, ibuprofen, FDA panels say. Medscape. https://www.medscape.com/viewarticle/895722. Published 2018. Accessed April 19 2019.
53. Derry S, Rice AS, Cole P, Tan T, Moore RA. Topical capsaicin (high concentration) for chronic neuropathic pain in adults. The Cochrane database of systematic reviews. 2017;1:CD007393.
54. ProCon.org. 36 legal medical marijuana states and DC. https://medicalmarijuana.procon.org/view.resource.php?resourceID=000881. Accessed February 1, 2021.
55. Rahn EJ, Zvonok AM, Thakur GA, Khanolkar AD, Makriyannis A, Hohmann AG. Selective activation of cannabinoid CB2 receptors suppresses neuropathic nociception induced by treatment with the chemotherapeutic agent paclitaxel in rats. J Pharmacol Exp Ther. 2008;327(2):584-591.
56. National Academies of Science. In: The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. Washington (DC) 2017.
57. Mucke M, Phillips T, Radbruch L, Petzke F, Hauser W. Cannabis-based medicines for chronic neuropathic pain in adults. The Cochrane database of systematic reviews. 2018;3:CD012182.
58. Kraft B, Frickey NA, Kaufmann RM, et al. Lack of analgesia by oral standardized cannabis extract on acute inflammatory pain and hyperalgesia in volunteers. Anesthesiology. 2008;109(1):101-110.
59. Wallace M, Schulteis G, Atkinson JH, et al. Dose-dependent effects of smoked cannabis on capsaicin-induced pain and hyperalgesia in healthy volunteers. Anesthesiology. 2007;107(5):785-796.
60. Hill KP, Palastro MD, Johnson B, Ditre JW. Cannabis and Pain: A Clinical Review. Cannabis Cannabinoid Res. 2017;2(1):96-104.
61. Stockings E, Campbell G, Hall WD, et al. Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies. Pain. 2018;159(10):1932-1954.
62. Hill KP. Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems: A Clinical Review. Jama. 2015;313(24):2474-2483.
63. Bachhuber MA, Saloner B, Cunningham CO, Barry CL. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. JAMA Intern Med. 2014;174(10):1668-1673.
64. Shover CL et al. Proc Natl Acad Sci USA. 2019;116:12624-12626
65. Narang S, Gibson D, Wasan AD, et al. Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. J Pain. 2008;9(3):254-264.
66. Walitt B, Klose P, Fitzcharles MA, Phillips T, Hauser W. Cannabinoids for fibromyalgia. The Cochrane database of systematic reviews. 2016;18(7).
67. Adel Y, Alexander SPH, Neuromolecular mechanisms of cannabis action. Adv Exp Med Biol. 2021;1264:15-28.
68. Schwenk ES, Viscusi ER, Buvanendran A, et al. Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Acute Pain Management From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Regional anesthesia and pain medicine. 2018;43(5):456-466.
69. Bruehl S. Complex regional pain syndrome. BMJ;2015:351:h2730.
70. Trescot AM, Datta S, Lee M, Hansen H. Opioid pharmacology. Pain physician. 2008;11(2 Suppl):S133-153.
71. Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: Results from the 2017 National Survey on Drug Use and Health HHS Publication No SMA 18-5068, NSDUH Series H-53. 2018.
72. Chu LF, Angst MS, Clark D. Opioid-induced hyperalgesia in humans: molecular mechanisms and clinical considerations. The Clinical journal of pain. 2008;24(6):479-496.
73. Angst MS, Clark JD. Opioid-induced hyperalgesia: a qualitative systematic review. Anesthesiology. 2006;104(3):570-587.
74. Ruta NS, Ballas SK. The opioid epidemic and sickle cell disease: Guilt by association. Pain Medicine 2016; 17: 1793–1798.
75. Brandow AM, Carroll CP, Creary S, Edwards-Elliot R, Glassberg J, Hurley RW, Kutlar A, Seisa M, Stinson J, Strouse JJ, Yusuf F, Zempsky W, Lang E. American Society of Hematology 2020 guidelines for sickle cell disease management of acute and chronic pain. Blood Adv. 2020;48:241-248.
76. Carroll CP. Opioid treatment for acute and chronic pain in patients with sickle cell disease. Neurosci Lett. 2020; Jan 1;714:134534. doi: 10.1016/j.neulet.2019.
77. Pedersen L, Borchgrevink PC, Breivik HP, Fredheim OM. A randomized, double-blind, double-dummy comparison of short- and long-acting dihydrocodeine in chronic non-malignant pain. Pain. 2014;155(5):881-888.
78. FDA blueprint for prescriber education for extended-release and long-acting opioid analgesics. In: Administration FaD, ed. Silver Springs, MD: US Department of Health and Human Services; 2017.
79. Food and Drug Administration. Extended-release and long-acting opioid analgesics shared system. http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM348818.pdf. Published 2015. Accessed.
80. Cicero TJ, Ellis MS, Surratt HL. Effect of abuse-deterrent formulation of OxyContin.
81. Chronis Manolis CBG, and William Shrank. Mandating Coverage Of Abuse-Deterrent Opioids Would Be A Costly Distraction From More Effective Solutions. In. Health Affairs2017.
82. Malonne H, Coffiner M, Sonet B, Sereno A, Vanderbist F. Efficacy and tolerability of sustained-release tramadol in the treatment of symptomatic osteoarthritis of the hip or knee: a multicenter, randomized, double-blind, placebo-controlled study. Clinical therapeutics. 2004;26(11):1774-1782.
83. Pharmacological management of persistent pain in older persons. J Am Geriatr Soc. 2009;57(8):1331-1346.
84. Zeng C, Dubreuil M, LaRochelle MR, et al. Association of Tramadol With All-Cause Mortality Among Patients With Osteoarthritis. Jama. 2019;321(10):969-982.
85. Drug Enforcement Administration. Tramadol information. Diversion Control Division, Drug & Chemical Evaluation Section. 2018.
86. Santos J, Alarcao J, Fareleira F, Vaz-Carneiro A, Costa J. Tapentadol for chronic musculoskeletal pain in adults. The Cochrane database of systematic reviews. 2015(5):CD009923.
87. Han B, Compton WM, Blanco C, Crane E, Lee J, Jones CM. Prescription Opioid Use, Misuse, and Use Disorders in U.S. Adults: 2015 National Survey on Drug Use and Health. Annals of internal medicine. 2017;167(5):293-301.
88. Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. Annals of internal medicine. 2010;152(2):85-92.
89. Jones JD, Mogali S, Comer SD. Polydrug abuse: a review of opioid and benzodiazepine combination use. Drug and alcohol dependence. 2012;125(1-2):8-18.
90. Tuteja AK, Biskupiak J, Stoddard GJ, Lipman AG. Opioid-induced bowel disorders and narcotic bowel syndrome in patients with chronic non-cancer pain. Neurogastroenterol Motil. 2010;22(4):424-430.
91. Hale M, Wild J, Reddy J, Yamada T, Arjona Ferreira JC. Naldemedine versus placebo for opioid-induced constipation (COMPOSE-1 and COMPOSE-2): two multicentre, phase 3, double-blind, randomised, parallel-group trials. Lancet Gastroenterol Hepatol. 2017;2(8):555-564.
92. Miller M, Sturmer T, Azrael D, Levin R, Solomon DH. Opioid analgesics and the risk of fractures in older adults with arthritis. J Am Geriatr Soc. 2011;59(3):430-438.
93. Dublin S, Walker RL, Jackson ML, et al. Use of opioids or benzodiazepines and risk of pneumonia in older adults: a population-based case-control study. J Am Geriatr Soc. 2011;59(10):1899-1907.
94. Li L, Setoguchi S, Cabral H, Jick S. Opioid use for noncancer pain and risk of myocardial infarction amongst adults. Journal of internal medicine. 2013;273(5):511-526.

95. Deyo RA, Smith DH, Johnson ES, et al. Prescription opioids for back pain and use of medications for erectile dysfunction. Spine. 1976;38(11):909-915.
96. Review. IfCaE. Abuse Deterrent Formulations of Opioids: Effectiveness and Value Final Evidence Report. 2017.
97. Lee TH. Zero Pain Is Not the Goal. Jama. 2016;315(15):1575-1577.
98. Brummett CM, Waljee JF, Goesling J, et al. New Persistent Opioid Use After Minor and Major Surgical Procedures in US Adults. JAMA Surg. 2017;152(6):e170504.
99. Calcaterra SL, Yamashita TE, Min SJ, Keniston A, Frank JW, Binswanger IA. Opioid Prescribing at Hospital Discharge Contributes to Chronic Opioid Use. Journal of general internal medicine. 2016;31(5):478-485.
100. Bateman BT, Franklin JM, Bykov K, et al. Persistent opioid use following cesarean delivery: patterns and predictors among opioid-naive women. Am J Obstet Gynecol. 2016;215(3):353 e351-353 e318.
101. Johnson SP, Chung KC, Zhong L, et al. Risk of Prolonged Opioid Use Among Opioid-Naive Patients Following Common Hand Surgery Procedures. The Journal of hand surgery. 2016;41(10):947-957 e943.
102. Brat GA, Agniel D, Beam A, et al. Postsurgical prescriptions for opioid naive patients and association with overdose and misuse: retrospective cohort study. BMJ. 2018;360:j5790.
103. Hall MJ, Schwartzman A, Zhang J, Liu X. Ambulatory Surgery Data From Hospitals and Ambulatory Surgery Centers: United States, 2010. Natl Health Stat Report. 2017(102):1-15.
104. Fishman SM. Responsible Opioid Prescribing: A Clinician's Guide, 2nd Ed. Washington, DC: Waterford Life Sciences; 2012.
105. Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. British journal of anaesthesia. 1997;78(5):606-617.
106. American Pain Society. Management of acute pain and chronic noncancer pain. http://americanpainsociety.org/education/enduring-materials. Accessed October 29 2018.
107. Frogner BK, Harwood K, Andrilla CHA, Schwartz M, Pines JM. Physical Therapy as the First Point of Care to Treat Low Back Pain: An Instrumental Variables Approach to Estimate Impact on Opioid Prescription, Health Care Utilization, and Costs. Health Serv Res. 2018;53(6):4629-4646.
108. Centers for Disease Control & Prevention. Module 2: Treating Pain Without Opioids. Course number WB2859. https://www.cdc.gov/drugoverdose/training/nonopioid. Published 2018. Accessed February 10, 2019.
109. 1American Geriatrics Society Beers Criteria Update Expert P. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2012;60(4):616-631.
110. Food and Drug Administration. Don't double up on acetaminophen. https://www.fda.gov/consumers/consumer-updates/dont-double-acetaminophen. Published 2018. Accessed July 12 2019.
111. Paice JA, Ferrans CE, Lashley FR, Shott S, Vizgirda V, Pitrak D. Topical capsaicin in the management of HIV-associated peripheral neuropathy. J Pain Symptom Manage. 2000;19(1):45-52.
112. Low PA, Opfer-Gehrking TL, Dyck PJ, Litchy WJ, O'Brien PC. Double-blind, placebo-controlled study of the application of capsaicin cream in chronic distal painful polyneuropathy. Pain. 1995;62(2):163-168.
113. Macintyre PE, Ready LB. Acute Pain Management: A Practical Guide, 2nd Ed. London: Saunders; 2003.
114. Goodman CW, Brett AS. Gabapentin and Pregabalin for Pain - Is Increased Prescribing a Cause for Concern? N Engl J Med. 2017;377(5):411-414.
115. Mathieson S, Maher CG, McLachlan AJ, et al. Trial of Pregabalin for Acute and Chronic Sciatica. N Engl J Med. 2017;376(12):1111-1120.
116. Blendon RJ, Benson JM. The Public and the Opioid-Abuse Epidemic. N Engl J Med. 2018;378(5):407-411.
117. Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, van der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. Pain. 2015;156(4):569-576.
118. Wu CL, Raja SN. Treatment of acute postoperative pain. Lancet. 2011;377(9784):2215-2225.
119. Chang AK, Bijur PE, Esses D, Barnaby DP, Baer J. Effect of a Single Dose of Oral Opioid and Nonopioid Analgesics on Acute Extremity Pain in the Emergency Department: A Randomized Clinical Trial. Jama. 2017;318(17):1661-1667.
120. Poonai N, Datoo N, Ali S, et al. Oral morphine versus ibuprofen administered at home for postoperative orthopedic pain in children: a randomized controlled trial. CMAJ. 2017;189(40):E1252-E1258.
121. Hunold KM, Esserman DA, Isaacs CG, et al. Side effects from oral opioids in older adults during the first week of treatment for acute musculoskeletal pain. Acad Emerg Med. 2013;20(9):872-879.
122. Solomon DH, Rassen JA, Glynn RJ, Lee J, Levin R, Schneeweiss S. The comparative safety of analgesics in older adults with arthritis. Archives of internal medicine. 2010;170(22):1968-1976.
123. Gil JA, Gunaseelan V, DeFroda SF, Brummett CM, Bedi A, Waljee JF. Risk of Prolonged Opioid Use Among Opioid-Naive Patients After Common Shoulder Arthroscopy Procedures. Am J Sports Med. 2019;47(5):1043-1050.
124. Miller M, Barber CW, Leatherman S, et al. Prescription opioid duration of action and the risk of unintentional overdose among patients receiving opioid therapy. JAMA internal medicine. 2015;175(4):608-615.
125. Kim N, Matzon JL, Abboudi J, et al. A Prospective Evaluation of Opioid Utilization After Upper-Extremity Surgical Procedures: Identifying Consumption Patterns and Determining Prescribing Guidelines. J Bone Joint Surg Am. 2016;98(20):e89.
126. Michigan Opioid Prescribing Engagement Network. Opioid prescribing recommendations for surgery. https://opioidprescribing.info/. Published 2019. Accessed May 1 2019.
127. Kroenke K, Bair MJ, Damush TM, et al. Optimized antidepressant therapy and pain self-management in primary care patients with depression and musculoskeletal pain: a randomized controlled trial. Jama. 2009;301(20):2099-2110.
128. Payne R, Anderson E, Arnold R, et al. A rose by any other name: pain contracts/agreements. The American journal of bioethics : AJOB. 2010;10(11):5-12.
129. Roskos SE, Keenum AJ, Newman LM, Wallace LS. Literacy demands and formatting characteristics of opioid contracts in chronic nonmalignant pain management. J Pain. 2007;8(10):753-758.
130. Fishman SM, Mahajan G, Wilsey B. Author response to: The trilateral opioid contract: bridging the pain clinic and the primary care physician through the opioid contract. J Pain Symptom Manage. 2003;25(5):403.
131. Chu J, Farmer B, Ginsburg B, et al. New York City emergency department discharge opioid prescribing guidelines. https://www1.nyc.gov/site/doh/providers/health-topics/opioid-prescribing-resources-for-emergency-departments.page. Published 2013. Accessed November 9 2018.
132. Cheng D, Majlesi N. Clinical practice statement: emergency department opioid prescribing guidelines for the treatment of noncancer related pain. Milwaukee, WI: American Academy of Emergency Medicine; 2013.
133. Thorson D, Biewen P, Bonte B, et al. Acute pain assessment and opioid prescribing protocol. Institute for Clinical Systems Improvement. https://www.icsi.org. Published 2014. Accessed November 9 2018.
134. Paone D, Dowell D, Heller D. Preventing misuse of prescription opioid drugs. City Health Information. 2011;30:23-30.
135. Cantrill SV, Brown MD, Carlisle RJ, et al. Clinical policy: critical issues in the prescribing of opioids for adult patients in the emergency department. Annals of emergency medicine. 2012;60(4):499-525.
136. Washington State Agency Medical Directors Group. Interagency Guideline on Opioid Dosing for Chronic Non-cancer Pain. 2010.
137. Webster LR, Dove B. Avoiding opioid abuse while managing pain. North Branch, MN: Sunrise River Press; 2007.
138. Knotkova H, Fine PG, Portenoy RK. Opioid rotation: the science and the limitations of the equianalgesic dose table. J Pain Symptom Manage. 2009;38(3):426-439.
139. Rudd RA, Seth P, David F, Scholl L. Increases in Drug and Opioid-Involved Overdose Deaths - United States, 2010-2015. MMWR Morbidity and mortality weekly report. 2016;65(5051):1445-1452.
140. VA/DoD. The management of opioid therapy for chronic pain working group. VA/DoD clinical practice guidelines for the management of opiod therapy for chronic pain. 2003(contract number: V101 (93)).
141. Food and Drug Administration. FDA approves first generic naloxone nasal spray to treat opioid overdose. FDA News Release. April 19 2019.
142. Frank JW, Lovejoy TI, Becker WC, et al. Patient Outcomes in Dose Reduction or Discontinuation of Long-Term Opioid Therapy: A Systematic Review. Annals of internal medicine. 2017;167(3):181-191.
143. Berna C, Kulich RJ, Rathmell JP. Tapering Long-term Opioid Therapy in Chronic Noncancer Pain: Evidence and Recommendations for Everyday Practice. Mayo Clin Proc. 2015;90(6):828-842.
144. Food and Drug Administration. FDA identifies harm reported from sudden discontinuation of opioid pain medicines and requires label changes to guide prescribers on gradual, individualized tapering. https://www.fda.gov/Drugs/DrugSafety/ucm635038.htm. Published 2019. Accessed April 19 2019.

145. American Psychiatric Association. DSM-5, Diagnostic and Statistical Manual of Mental Disorders: Fifth ed. Washington DC: American Psychiatric Association; 2013.
146. Wu LT, Zhu H, Swartz MS. Treatment utilization among persons with opioid use disorder in the United States. Drug and alcohol dependence. 2016;169:117-127.
147. National Academies of Sciences Engineering and Medicine. Medications for opioid use disorder save lives. The National Academies Press. 2019:doi: https://doi.org/10.17226/25310.
148. Kreek MJ. Methadone-related opioid agonist pharmacotherapy for heroin addiction. History, recent molecular and neurochemical research and future in mainstream medicine. Ann N Y Acad Sci. 2000;909:186-216.
149. Degenhardt L, Randall D, Hall W, Law M, Butler T, Burns L. Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: risk factors and lives saved. Drug and alcohol dependence. 2009;105(1-2):9-15.
150. Degenhardt L, Bucello C, Mathers B, et al. Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies. Addiction. 2011;106(1):32-51.
151. Sordo L, Barrio G, Bravo MJ, et al. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. BMJ. 2017;357:j1550.
152. Food and Drug Administration. FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants. www.fda.gov/Drugs/DrugSafety/ucm575307.htm. Published 2017. Accessed May 15 2019.
153. Kleber HD. Pharmacologic treatments for opioid dependence: detoxification and maintenance options. Dialogues Clin Neurosci. 2007;9(4):455-470.
154. Dahan A, Yassen A, Romberg R, et al. Buprenorphine induces ceiling in respiratory depression but not in analgesia. British journal of anaesthesia. 2006;96(5):627-632.
155. Connery HS. Medication-assisted treatment of opioid use disorder: review of the evidence and future directions. Harv Rev Psychiatry. 2015;23(2):63-75.
156. American Society of Addiction Medicine. Buprenorphine Waiver Management. https://www.asam.org/resources/practice-resources/buprenorphine-waiver-management#NPPA. Published 2019. Accessed May 15 2019.
157. Fareed A, Patil D, Scheinberg K, et al. Comparison of QTc interval prolongation for patients in methadone versus buprenorphine maintenance treatment: a 5-year follow-up. Journal of addictive diseases. 2013;32(3):244-251.
158. Rosenthal RN, Lofwall MR, Kim S, et al. Effect of Buprenorphine Implants on Illicit Opioid Use Among Abstinent Adults With Opioid Dependence Treated With Sublingual Buprenorphine: A Randomized Clinical Trial. Jama. 2016;316(3):282-290.
159. Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A. Oral naltrexone maintenance treatment for opioid dependence. The Cochrane database of systematic reviews. 2011(4):CD001333.
160. Binswanger IA, Glanz JM. Potential Risk Window for Opioid Overdose Related to Treatment with Extended-Release Injectable Naltrexone. Drug Saf. 2018;41(10):979-980.
161. Kakko J, Svanborg KD, Kreek MJ, Heilig M. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial. Lancet. 2003;361(9358):662-668.
162. Clark RE, Baxter JD, Aweh G, O'Connell E, Fisher WH, Barton BA. Risk Factors for Relapse and Higher Costs Among Medicaid Members with Opioid Dependence or Abuse: Opioid Agonists, Comorbidities, and Treatment History. J Subst Abuse Treat. 2015;57:75-80.
163. Krupitsky E, Nunes EV, Ling W, Illeperuma A, Gastfriend DR, Silverman BL. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. Lancet. 2011;377(9776):1506-1513.
164. Schwartz RP, Kelly SM, O'Grady KE, Gandhi D, Jaffe JH. Randomized trial of standard methadone treatment compared to initiating methadone without counseling: 12-month findings. Addiction. 2012;107(5):943-952.
165. Fiellin DA, Barry DT, Sullivan LE, et al. A randomized trial of cognitive behavioral therapy in primary care-based buprenorphine. The American journal of medicine. 2013;126(1):74 e11-77.
166. Ling W, Hillhouse M, Ang A, Jenkins J, Fahey J. Comparison of behavioral treatment conditions in buprenorphine maintenance. Addiction. 2013;108(10):1788-1798.
167. Weiss RD, Potter JS, Fiellin DA, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial. Arch Gen Psychiatry. 2011;68(12):1238-1246.
168. Schwartz RP. When Added to Opioid Agonist Treatment, Psychosocial Interventions do not Further Reduce the Use of Illicit Opioids: A Comment on Dugosh et al. Journal of addiction medicine. 2016;10(4):283-285.
169. Nosyk B, Sun H, Evans E, et al. Defining dosing pattern characteristics of successful tapers following methadone maintenance treatment: results from a population-based retrospective cohort study. Addiction. 2012;107(9):1621-1629.
170. Substance Abuse and Mental Health Services Administration. Buprenorphine. https://www.samhsa.gov/medication-assisted-treatment/treatment/buprenorphine. Published 2019. Accessed May 15 2019.
171. Wakeman SE, Barnett ML. Primary Care and the Opioid-Overdose Crisis - Buprenorphine Myths and Realities. N Engl J Med. 2018;379(1):1-4.
172. Kennedy-Hendricks A, McGinty EE, Barry CL. Effects of Competing Narratives on Public Perceptions of Opioid Pain Reliever Addiction during Pregnancy. J Health Polit Policy Law. 2016;41(5):873-916.
173. Kennedy-Hendricks A, Busch SH, McGinty EE, et al. Primary care physicians' perspectives on the prescription opioid epidemic. Drug and alcohol dependence. 2016;165:61-70.
174. Woo J, Bhalerao A, Bawor M, et al. "Don't Judge a Book Its Cover": A Qualitative Study of Methadone Patients' Experiences of Stigma. Subst Abuse. 2017;11:1178221816685087
175. Words matter handout. https://d14rmgtrwzf5a.cloudfront.net/sites/default/files/words_matter_handout.pdf. Accessed May 16 2019.
176. Minozzi S, Amato L, Bellisario C, Ferri M, Davoli M. Maintenance agonist treatments for opiate-dependent pregnant women. The Cochrane database of systematic reviews. 2013(12):CD006318.
177. Kaltenbach K, Finnegan LP. Developmental outcome of children born to methadone maintained women: a review of longitudinal studies. Neurobehav Toxicol Teratol. 1984;6(4):271-275.
178. Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. N Engl J Med. 2010;363(24):2320-2331.
179. Metz VE, Brown QL, Martins SS, Palamar JJ. Characteristics of drug use among pregnant women in the United States: Opioid and non-opioid illegal drug use. Drug and alcohol dependence. 2018;183:261-266.
180. Alford DP, Compton P, Samet JH. Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. Annals of internal medicine. 2006;144(2):127-134.
181. Jacobsen J, Jackson V, Dahlin C, et al. Components of early outpatient palliative care consultation in patients with metastatic nonsmall cell lung cancer. J Palliat Med. 2011;14(4):459-464.
182. Forrow L, Smith HS. Pain management in end of life: palliative care. In: Warfield CA BZ, ed. Principles & Practice of Pain Medicine. 2nd ed. New York, NY: McGraw-Hill; 2004.
183. Morita T, Tsunoda J, Inoue S, Chihara S. Effects of high dose opioids and sedatives on survival in terminally ill cancer patients. J Pain Symptom Manage. 2001;21(4):282-289.
184. Sykes N, Thorns A. The use of opioids and sedatives at the end of life. The Lancet Oncology. 2003;4(5):312-318.
185. Paice JA, Ferrell B. The management of cancer pain. CA Cancer J Clin. 2011;61(3):157-182.
186. Keefe FJ, Abernethy AP, L CC. Psychological approaches to understanding and treating disease-related pain. Annu Rev Psychol. 2005;56:601-630.

EFFECTIVE MANAGEMENT OF ACUTE AND CHRONIC 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. Nonpharmacologic and self-management treatment options have been found to be effective alone or as part of a comprehensive pain management plan for which types of pain?
- A. Nociceptive and neuropathic pain.
- B. Acute pain > 48 hours after tissue trauma.
- C. Neuropathic and chronic pain.
- D. Musculoskeletal and chronic pain.

2. What is the maximum recommended daily dose of acetaminophen for healthy adult patients?
- A. 2500 mg.
- B. 3000 mg.
- C. 3500 mg.
- D. 4000 mg.

3. Which non-opioid analgesic has been successfully used to treat such acute pain conditions as sickle cell crises, renal colic, and trauma?
- A. Ketamine.
- B. Cannabis.
- C. Capsaicin.
- D. Anticonvulsants.

4. Which of the following topics should be routinely covered as part of patient education about opioid analgesics?
- A. Background information about acute vs. chronic pain.
- B. Criteria for Opioid Use Disorder.
- C. Safe medication disposal.
- D. Difference between nociceptive and neuropathic pain.

5. Which of the following is an example of a functional goal?
- A. Reduced anxiety about pain.
- B. Reduced need for rescue analgesia.
- C. Reduced daily dose of opioid analgesic.
- D. Resumed sexual relations.

6. Which of the following is a possible reason for prescribing naloxone to a patient who has been prescribed an opioid analgesic?
- A. The patient is taking a dose of an opioid > 50 MMED.
- B. The patient has recently entered prison.
- C. The patient has history of hypertension.
- D. The patient has a concurrent prescription for an SSRI antidepressant.

7. According to the Centers for Disease Control and Prevention, what amount of opioid analgesic is appropriate for most painful conditions?
- A. 2-day supply.
- B. 3-day supply.
- C. 5-day supply.
- D. 7 day supply.

8. Which of the following medications is a full mu-receptor agonist used to treat Opioid Use Disorder?
- A. Methadone.
- B. Buprenorphine.
- C. Extended-release naltrexone.
- D. Naloxone.

9. Which of the following medications can be self-administered by patients with a medication obtained from a regular pharmacy?
- A. Methadone.
- B. Buprenorphine.
- C. Extended-release naltrexone.
- D. Naloxone.

10. For which of the following must clinicians obtain a special waiver from the DEA prior to being able to prescribe the medication?
- A. Methadone.
- B. Buprenorphine.
- C. Extended-release naltrexone.
- D. Naloxone.

NOTES

ALTERNATIVES TO OPIOIDS FOR PAIN MANAGEMENT

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

This course is designed for all physicians and health care professionals involved in the treatment and monitoring 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

This CME learning activity is designed to increase physician knowledge and skills about guideline-recommended principles for effectively managing chronic and acute pain conditions with non-opioid pain treatments with a focus non-opioid options for four common painful conditions: osteoarthritis, low-back pain, diabetic neuropathy, and fibromyalgia.

LEARNING OBJECTIVES

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

1. Explain the potential value of creating and using function-based treatment plans for patients with chronic pain conditions.
2. Discuss the general principles for initiating treatments for acute or chronic pain conditions.
3. Describe examples of non-opioid analgesic options for managing acute pain.
4. Describe examples of non-opioid analgesic options for managing chronic non-cancer pain.

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

Paul J. Christo, MD, MBA
Director, Multidisciplinary Pain Fellowship Program
Associate Professor of Anesthesiology and Critical Care Medicine
The Johns Hopkins University School of Medicine

Annette Skopura, PHD
Medical Writer
EnlightenMed

ACTIVITY PLANNER

Michael Brooks
CME Director
InforMed

COURSE SATISFIES

2

Pain Management and Addiction Disorders

KENTUCKY SPECIAL APPROVAL:

This course satisfies two (2) CME credit hours in pain management and addiction disorders.

The Kentucky Board of Medical Licensure requires physicians who prescribe or dispense controlled substances in Kentucky to complete four and one-half (4.5) hours of CME relating to the use of KASPER, pain management, addiction disorders, or a combination of two or more of those subjects.

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.

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:

- Annette Skopura, PHD
- Michael Brooks

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

- Paul J. Christo, MD, MBA has received honoraria from GlaxoSmithKline, Daiichi Sankyo, and BTG International.

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

Across specialties, physicians are concerned about opioid pain medication misuse, they find managing patients with chronic pain stressful, express concern about patient addiction, and say they have insufficient training in prescribing opioids.[1] It is increasingly understood that although opioids can effectively control pain, addiction can be a consequence of prolonged use, and long-term opioid therapy is often overprescribed for patients with chronic non-cancer pain.[2]

Many of the problematic issues surrounding the use of opioids for chronic pain are equally compelling and urgent in the treatment of acute pain. For example, a number of studies demonstrate an increased risk of new persistent opioid use in opioid-naïve patients after having been prescribed opioids for acute pain.[3-6]

Physicians are constantly challenged to provide optimum pain relief for those suffering from acute and chronic pain in an era dominated by a profound opioid crisis. In 2020 an average of 252 people were dying every day from opioid-related overdoses.[7]

In this context it is essential that clinicians become familiar with the wide array of non-opioid analgesic treatment options (both pharmacologic and non-pharmacologic) for acute and chronic pain conditions. Clinicians need to understand the relatively recent evidence showing that opioids may not be very effective for relieving chronic pain in the long-term and, in fact, may be associated with increased pain, reduced functioning, and opioid dependence.[8,9]

This CME learning activity focuses on the evidence supporting the effectiveness of non-opioid therapies, suggests strategies for assessing and managing patients with both chronic and acute pain, and takes an in-depth look at non-opioid options for four common painful conditions: osteoarthritis, low-back pain, diabetic neuropathy, and fibromyalgia.

General strategies for pain management

The importance of function-based pain treatment plans

Formal treatment plans are seldom needed for treating acute pain conditions, but they may be extremely valuable when treating patients with chronic pain, regardless of the specific treatment options being considered. The plans should include the goals of therapy and should be written carefully because pain is inherently subjective. Since pain cannot be measured objectively, framing treatment goals solely in terms of pain relief means that such goals cannot be objectively confirmed.

Although a patient's subjective pain and suffering are obviously important, only the functional impact of the pain can be measured and used to create objective treatment goals. This impact takes many forms, including reductions or dysfunctions in physical activity, concentration, emotional stability, interpersonal relationships, and sleep. These impacts, in turn, degrade functioning at work or in the home, which can lead to depression, anxiety, insomnia, and even suicide. Even relatively modest pain reductions can lead to significant functional improvements.[10] A 20% reduction in a pain score (i.e., roughly two points on the standard 0-10 pain scale) may be acceptable if it produces significant functional benefits for a patient.

Function-based treatment goals, rather than pain relief goals, offer two primary advantages to clinicians:

- Treatment decisions are based on outcomes that can be objectively demonstrated to both clinician and patient (and, possibly, to the patient's family)
- Individual differences in pain tolerance become secondary to the setting and monitoring of treatment goals, since subjectively perceived levels of pain are not the primary focus in determining functionality.

Function-based treatment plans are especially valuable in the context of prescribing opioid pain medications, because such goals may help determine whether a patient has an opioid use disorder, but they serve many useful purposes even when treatments do not involve opioids. Functional decline itself may result from a range of problems, including inadequate pain relief, non-adherence to a regimen, function-limiting side effects, or untreated affective disorders. Sometimes impaired functioning is the result of an opioid use disorder (OUD), and these objective results may shed valuable light on an otherwise confusing presentation of pain symptoms.

It's important to set realistic functional goals. Progress in restoring function is usually slow, irregular, and gains are typically incremental. Chronic non-cancer pain is often marked by long-standing physical and psychological deconditioning, and recovery may require reconditioning that may take weeks, months, or years. It is much better to set goals that are slightly too low than slightly too high. Raising goals after a patient has "succeeded" in achieving them is far more motivational and encouraging than lowering goals after a patient has "failed" (although one should not use the word "fail" or "failed" in actual practice).

Treatment initiation

A central tenet of pain management, whether for acute or chronic pain, is to aim for a tolerable level of pain that allows the patient maximum physical and emotional functioning with the lowest risk of side effects, progression to chronic pain, or misuse or abuse.[10] This requires a careful balancing of patient-related factors (e.g., comorbidities, medical history, risk of abuse) and drug-related factors (e.g., potency, mechanism of action, expected side effects). A commonly-recommended way to achieve this balance is with multimodal analgesia, in which several therapeutic approaches are used, each acting on different pain pathways, which can reduce dependence on a single medication and may reduce or eliminate the need for opioids and attendant risks/side effects.[11]

Multimodal analgesia can produce synergistic effects, reduce side effects, or both. One example of multimodal analgesia is the use of both an NSAID and acetaminophen, plus physical approaches (e.g., cold, compression, or elevation) to manage postoperative pain. Demonstrated benefits of multimodal analgesia include earlier ambulation, earlier oral intake, and earlier hospital discharge for postoperative patients, as well as higher levels of participation in activities necessary for recovery (e.g., physical therapy).[11]

The many pharmacologic and non-pharmacologic approaches to treating acute and chronic pain should be employed using the following general principles:

- Identify and treat the source of the pain, if possible, although pain treatment can begin before the source is determined
- Use the simplest approach to pain management first. This generally means using non-pharmacologic approaches as much as possible and/or trying medications with the least severe potential side effects, and at the lowest effective doses
- Create function-based, individualized treatment plans if therapy is expected to last longer than a week
- Reserve opioid analgesics for moderate-to-severe acute pain unresponsive to non-opioid therapies or moderate-to-severe chronic pain in patients who have been assessed for risk of abuse or dependence and for whom previous trials of both drug and non-drug approaches have failed to provide an adequate response.

Managing patient expectations

Patients in pain are understandably worried that the pain will persist or get worse with time. Physicians can reduce such fears and set realistic expectations for treatment effectiveness and healing with clear, compassionate communication couched in terms patients can easily understand. It can be helpful, for example, to share with patients the fact that most forms of acute pain (e.g., nonspecific low back pain) are self-limiting, subside within weeks, and do not require invasive interventions. (In a systematic review of 15 prospective cohort studies, 82% of people who stopped work due to acute low back pain returned to work within one month.)[12]

Regular communication with patients may be helpful. A systematic review of 14 controlled trials of patient education interventions for low back pain showed that structured messaging by providers can reassure patients more than usual care/control education both in the short and long term.[13] Messaging was significantly more reassuring to patients when delivered by physicians as opposed to other primary care practitioners, and such communication reduced the frequency of primary care visits.

Non-opioid options for acute pain

The initial choice for treating acute pain conditions should not involve opioids because, as noted above, many of the problems and risks associated with managing chronic pain with opioids are also in play when managing acute pain with opioids. For example, a number of studies demonstrate increased risk of new persistent opioid use in opioid-naïve patients after having been prescribed opioids for acute pain.[3-6] Although the risk of opioid misuse in patients prescribed opioids for acute post-surgical or post-procedural pain is relatively small (roughly 0.6% per year)[14], the volume of such procedures (approximately 48 million ambulatory surgeries or procedures in 2010)[15] means large numbers of patients (i.e., approximately 160,000) may develop misuse, abuse, or overdose every year.

Non-drug treatments for acute pain

The degree to which it is possible to treat acute pain without opioids depends on the severity, type, and origin of the pain, but many non-pharmacological approaches can be very effective and their use avoids the potential side effects and risks associated with pharmacological interventions.[16]

Physical methods of pain management can be helpful in all phases of care, including immediately after tissue trauma (e.g., rest, application of cold, compression, elevation) and later in the healing period (e.g., exercises to regain strength and range of motion).

Non-pharmacologic methods can include:[16]

- Application of cold (generally within first 24 hours) or heat
- Compression
- Elevation
- Immobilization
- Relaxation exercises
- Distraction/guided imagery
- Acupuncture
- Massage
- Electroanalgesia (e.g., transcutaneous electrical nerve stimulation)
- Physical therapy
- Yoga

Physical therapy may be useful for a range of musculoskeletal issues and can be helpful in recovering from acute pain-producing traumas initially treated with other methods. A 2018 study reported that patients with low back pain who first consulted a physical therapist were less likely to receive an opioid prescription compared to those who first saw their primary care physician.[17]

Exercise therapy can take many forms, including walking, swimming or in-water exercise, weight training, or use of aerobic or strength-training equipment. According to a review by the Centers for Disease Control and Prevention (CDC), conditions that may improve with exercise therapy include low back pain, neck pain, hip and knee osteoarthritis pain, fibromyalgia, and migraine.[18]

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

Non-opioid pharmacologic treatments for acute pain

Acetaminophen and NSAIDs

Mild-to-moderate acute pain generally responds well to oral non-opioids (e.g., acetaminophen, non-steroidal anti-inflammatories [NSAIDs], and topical agents).

Although they are weaker analgesics than opioids, acetaminophen and NSAIDs do not produce tolerance, physical dependence, or addiction and they do not induce respiratory depression or constipation. The choice of medication may be driven by patient risk factors for drug-related adverse effects. If acetaminophen or NSAIDs are contraindicated or have not sufficiently eased the patient's pain or if functioning has not improved despite maximal or combination therapy, other drug classes (e.g., opioids) may be considered.

Non-opioid analgesics are not without risk, particularly in older patients. The FDA recommends that the total adult daily dose not exceed 4,000 mg in patients without liver disease (with a lower ceiling for older adults – generally 3,000 mg).[19]

Case Study 1

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

Ruth is a 66 year old female with history of right knee pain from osteoarthritis that was becoming progressively worse and limiting her activity. Ruth lives in a two-story home and has enjoyed sports and being physically active. She underwent a right total knee replacement three days ago and is scheduled to start physical and occupational therapy soon. Ruth was discharged with a prescription for oxycodone 10 mg q4-6 hrs. which she has been taking, although she complains of constipation. She is afraid to take more oxycodone because she says she's afraid of becoming addicted, but is also anxious about getting off the opioids. She has come for a check of the incisions, which are healing well, but she is very worried that the physical therapy will be too painful to bear.

1. **What might you be able to communicate to Ruth to help allay her anxieties?**_____

2. **What alternatives to the oxycodone might you suggest that Ruth try?**_____

3. **How can you and Ruth create a plan, or record, that will provide some objective measures of progress, both in terms of pain relief as well as function?**_____

The FDA currently sets a maximum limit of 325 mg of acetaminophen in prescription combination products (e.g., hydrocodone and acetaminophen) in an attempt to limit liver damage and other potential ill effects of these products.[32]

Topical capsaicin and salicylates can both be effective for short term pain relief and generally have fewer side effects than oral analgesics, but their long-term efficacy is not well studied.[20,21] The burning sensation from topical capsaicin can be difficult to tolerate. Topical aspirin can help reduce pain from acute herpes zoster infection.[22] Topical NSAIDs and lidocaine may also be effective for short-term relief of superficial pain with minimal side effects. Topical agents can be simple and effective for reducing pain associated with wound dressing changes, debridement of leg ulcers, and other sources of superficial pain.[22]

Anticonvulsants

Anticonvulsants, such as gabapentin, pregabalin, oxcarbazepine, and carbamazepine, are often prescribed for chronic neuropathic pain (e.g., post-herpetic neuralgia and diabetic neuropathy) although evidence for efficacy in acute pain conditions is weak.[23] A 2017 trial, for example, randomized 209 patients with sciatica pain to pregabalin 150 mg/day titrated to a maximum of 600 mg/day vs. placebo for 8 weeks.[24] At 8 weeks there was no significant difference in pain between groups (mean leg pain intensity on a 0-10 scale 3.7 with pregabalin vs. 3.1 with placebo, P=0.19).

Potential side effects of anticonvulsants include sedation, dizziness, and peripheral edema. Pregabalin and gabapentin also have some abuse potential in the general population because some users report euphoric effects. Abrupt cessation of anticonvulsants may precipitate withdrawal symptoms.[23]

Ketamine

Ketamine has been used as a general anesthetic since the 1960s, but its use in subanesthetic concentrations for analgesia has grown rapidly in recent years, due, in part, to efforts to reduce the risks of chronic opioid use.[25] Ketamine has been successfully used to treat such acute pain conditions as sickle cell crises, renal colic, and trauma.[25] In 2018 the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists released joint recommendations for subanesthetic ketamine (including transdermal ketamine) for acute pain with the following guidelines:[25]

- Indications
  - Perioperative use in surgery with moderate to severe postoperative pain
  - Perioperative use in patients with opioid tolerance
  - Adjunct in opioid-tolerant patients with sickle cell crisis
  - Adjunct in patients with obstructive sleep apnea
- Dose
  - Bolus IV: up to 0.35 mg/kg
  - Infusion: up to 1 mg/kg/hour
- Contraindications
  - Poorly-controlled cardiovascular disease
  - Pregnancy
  - Psychosis
  - Severe hepatic disease
  - Elevated intracranial pressure
  - Elevated intraocular pressure

Non-opioid options for chronic non-cancer pain

Non-pharmacologic approaches

Physical rehabilitative and surgical approaches, procedural therapies (e.g., injections, nerve blocks), complementary therapies, and use of approved/cleared medical devices may all be potentially effective either alone or as part of a comprehensive pain management plan, particularly for musculoskeletal pain and chronic pain.[26]

Movement-based options

Muscle-strengthening, stretching, and aerobic exercise (e.g., walking, aquatics) may all be helpful for patients in chronic pain. Recommended exercise programs typically occur one to three times a week for a total of 60-180 minutes per week, but any regimen must be carefully tailored to a patient's existing level of physical conditioning, comorbidities, and cognitive status.[27-29]

Additional movement-based options include:

- **Physical therapy** supervised by a licensed physical therapist, which can include resistance, aerobic, balance, and flexibility exercises as well as elements of massage, manipulation, or transcutaneous electrical nerve stimulation.
- **Tai chi,** a mind-body practice that combines controlled movements, meditation, and deep breathing. "Chair tai chi" can be an option for patients with limited mobility.
- **Yoga,** exercises or a series of postures designed to align muscle and bones, and increase strength and flexibility. It can also relax mind and body through breathing exercises and meditation. Gentler forms of yoga that may be more appropriate for older patients include Iyengar, Hatha, or Viniyoga.

Weight loss

Some pain syndromes, such as knee osteoarthritis, are worsened by obesity. For some patients, pain due to this condition is improved by reducing body weight, which lowers physical stresses on affected joints. The goal of body weight reduction is a baseline weight loss of 7%-10% by calorie reduction and increased activity using a balanced diet with less than 30% of calories from fat, 15%-20% from protein, and 45%-60% from carbohydrates.[30]

Passive options

Acupuncture involves the stimulation of specific points on the body, most often involving skin penetration with fine metallic needles manipulated by hand but sometimes also including electrical stimulation or low intensity laser therapy. Potential adverse events include minor bruising and bleeding at needle insertion sites.[31]

Transcutaneous electrical nerve stimulation (TENS) involves mild electrical pulses applied cutaneously. The electrical stimulation from TENS may block or disrupt pain signals to the brain, reducing pain perception. TENS machines can be used at home or in conjunction with other interventions like physical therapy.

Cognitive and behavioral options

Cognitive behavioral therapy (CBT) is a structured, time-limited (typically 3-10 weeks) intervention focused on how thoughts, beliefs, attitudes, and emotions influence pain and can help patients use their minds to control and adapt to pain. This therapy includes setting goals, often with recommendations to increase activity to reduce feelings of helplessness.[32]

Meditation

Mindfulness meditation programs typically include a time-limited (8 weeks; range 3-12 weeks) trainings with group classes and home meditation. The objective is to inculcate a long-term practice that helps patients refocus their minds on the present, increase awareness of self and surroundings, and reframe experiences.[33,34]

Injection-based interventions

Several types of injection therapies can help to ease pain and provide durable relief. In the spine, multiple pain generators can be targeted: facet joints, discs, nerves, and muscles.[35] Parts of the sympathetic nervous system can be accessed with therapeutic injections for patients with visceral pain, and injections into specific joints with steroid or viscosupplements can reduce joint pain.[35] Epidural steroid injections, radiofrequency ablation, pulsed and cooled radiofrequency procedures, and neuromodulation treatments (spinal cord stimulation, peripheral nerve stimulation) all have an important role in reducing chronic pain.[36-38]

Non-opioid drug approaches

In addition to the non-opioid pharmacologic options reviewed above, evidence suggests efficacy for the following drug classes in the context of treating chronic non-cancer pain:

- Antidepressants
  - serotonin and/or norepinephrine reuptake inhibitors
  - tricyclic antidepressants (TCAs)
  - selective serotonin reuptake inhibitors (SSRIs)
- Topical lidocaine or capsaicin
- Possible cannabinoid-based therapies

Serotonin norepinephrine reuptake inhibitors

SNRIs such as duloxetine, venlafaxine, and milnacipran are characterized by a mixed action on norepinephrine and serotonin, though their exact mechanism of action for pain reduction is unknown. Side effects (e.g., nausea, dizziness, and somnolence) may limit treatment. Routine monitoring for blood pressure (duloxetine and venlafaxine), heart rate (venlafaxine), and drug interactions (duloxetine) is recommended. SNRIs can be very helpful in patients who have central sensitization.

TCAs

TCAs inhibit reuptake of norepinephrine and serotonin, but their mechanism of action for pain relief is unknown. Examples of TCAs studied for the management of chronic pain include amitriptyline, desipramine, and nortriptyline. Side effects, such as anticholinergic effects (e.g., dry mouth, constipation, dizziness) and QTc prolongation can limit the use of TCAs in elderly patients. The majority of side effects occur at the typically higher doses used to treat depression.

SSRIs

SSRIs, such as citalopram, fluoxetine, and paroxetine, block the reuptake of serotonin in the brain, making more serotonin available in the synapse. The mechanism of SSRIs for pain remains unknown. Compared to SNRIs and TCAs, there is relatively little evidence to support the use of SSRIs in treating chronic pain conditions.[39] Potential side effects of SSRIs include weight gain, sexual dysfunction, and QTc prolongation, especially with citalopram.

Topical lidocaine

Topical lidocaine inhibits the conduction of nociceptive nerve impulses. Irritation at the application site is the most common side effect. The most common products for chronic pain management are lidocaine 5% patches, available by prescription, and lidocaine 4% patches available OTC.

Cannabinoid preparations

With medical cannabis now legal in 34 states and recreational use legal in 11 states and the District of Columbia (as of May, 2020)[40], there has been increased interest among patients for the use of cannabis or cannabis derivatives (e.g., cannabidiol [CBD]) for chronic pain relief. The CB1 and CB2 receptors have been shown to mediate the analgesic effects of cannabinoids[41] and some evidence suggests a potential benefit for chronic pain. A 2017 National Academies of Science report, for example, concluded that "conclusive or substantial evidence" supports a beneficial role for cannabis or cannabinoids for treating chronic pain,[42] and a 2018 Cochrane review of the existing literature evaluating cannabinoids (cannabis, CBD, or combinations) suggests that these agents are moderately effective for neuropathic pain with adverse effects that are less than, or comparable to, existing non-opioid analgesics.[43]

A systematic review of both randomized trials (47) and observational studies (57) in patients with chronic non-cancer pain published through July 2017 found moderate evidence that cannabinoids can exert analgesia.[44] Cannabis preparations, however, may pose both short-term and long-term risks. Short-term effects include impaired memory, motor coordination, and judgment. Paranoid ideation and psychotic symptoms, while rare, may occur with high doses of THC. Possible long-term effects include impaired brain development in young adults, potential for habituation, increased risk of anxiety or depression, and cannabis use disorder. Abrupt cessation of marijuana in long-term users may cause withdrawal symptoms such as anxiety, irritability, craving, dysphoria, and insomnia. There is an increased risk of chronic bronchitis, respiratory infections, and pneumonia with inhaled products.[45]

FDA-approved cannabinoids include dronabinol (Marinol), indicated for second-line treatment of chemotherapy-induced nausea and vomiting, and anorexia-associated weight loss in patients with HIV. Nabilone (Cesamet and Syndros) are indicated for chemotherapy-induced nausea and vomiting. Common side effects include dizziness/vertigo and euphoria. Dronabinol may cause nausea/vomiting, abdominal pain, and abnormal thinking. Nabilone may cause ataxia and dry mouth.[45,46,47] None of these are indicated for the treatment of pain, although some emerging evidence suggests that THC has analgesic and/or antispasmodic properties that can ameliorate some types of acute or chronic pain (e.g., lumbar pain/spasms).[42]

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

Disease-specific guidance

Osteoarthritis

Exercise and physical activity

A 2018 Cochrane review of 21 randomized trials including 2,372 patients with hip, knee, or hip and knee osteoarthritis (OA) found that exercise-based interventions reduced pain scores (on a 0-20 scale) by a mean of 1.2 points after about 45 weeks (6% absolute reduction compared to non-exercise treatments; 95% CI: -9% to -4%).[48] Physical functioning improved by 5.6 points on a 0-100 scale but the result was not significant (5.6% absolute reduction; 95% CI: -7.6% to 2%). Exercise interventions were diverse and included tai chi, physical therapy, strength training, and aerobic exercise (e.g., walking, cycling).

The importance of clear patient education about the potential benefits of exercise for patients with OA was suggested by results from a review of 12 qualitative studies, conducted as part of the same Cochrane review. The authors noted that patients are often worried that they might hurt themselves by exercising, or that the exercise might worsen their symptoms. Patients wanted providers to give better information about the safety and value of exercise as well as exercise recommendations tailored to individual patient needs and abilities.[48]

A 2019 trial randomized 171 adults aged ≥60 years with knee OA to a 12-week home-based exercise intervention plus health education vs. health education only.[49] The exercise intervention involved group training sessions plus at-home strength and flexibility exercises to be done 30-40 minutes/day, three days per week. At 12-week follow-up, mean pain scores on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) dropped 3.06 points in the intervention group vs. 1.46 points in the control group (P=0.007), and stiffness level decreased one level vs. no change (P=0.008).

Weight loss

Weight loss interventions studied for OA typically focus on joint stress or injury rather than pain. However, in the Intensive Diet and Exercise for Arthritis (IDEA) randomized trial, the investigators assessed pain as a secondary outcome.[30] The study included 545 older adults with knee OA and overweight randomized to one of three approaches: diet plus exercise, diet alone, or exercise alone. At 18 months the diet plus exercise intervention was associated with greater pain reduction than the diet or exercise alone groups. In the diet plus exercise group 38% of patients reported little or no pain compared with 20% and 22% of patients with diet or exercise alone, respectively (P=0.002 for both comparisons).[30]

WOMAC function scores improved significantly in the diet plus exercise group compared to the diet group and the exercise alone group.[30]

Case Study 2

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

Mike, 21, presents to a primary care clinic as a new patient. On his intake form, the clinic nurse has written that the patient made an urgent appointment yesterday with a chief complaint of "back pain." When you enter the room, Mike appears not to be in acute distress as he is texting on his phone. The patient briefly winces when he stands up from his chair to shake your hand. He sits back down and tells he is generally healthy but that two years ago, he fell while working on a roof. You express concern, but he shrugs it off, saying that he fell into the bushes, which broke his fall, but that he did hurt his back. At the Emergency Room the ER attending diagnosed him with a muscle injury, prescribed oxycodone, and sent him home to rest. However, the patient says he continues to have chronic back pain and would like another prescription for oxycodone so that he can go back to work.

1. **Given the subjective nature of pain, how can a clinician more objectively assess the kind of pain reported by patients such as Mike?**

2. **What kinds of non-opioid treatments might you suggest Mike try before writing a new prescription for oxycodone?**

3. **What types of functional goals might be appropriate as part of a treatment plan for Mike?**

Tai chi

A meta-analysis of 15 randomized trials in patients with musculoskeletal pain (80% OA) found tai chi to be moderately effective in improving both pain and disability at up to 3 months compared to no intervention.[50] No statistically significant differences were observed at 3 months to 1 year, or >1 year.

A randomized trial with 204 adults with symptomatic knee OA compared 12 weeks of twice-weekly tai chi vs. standard physical therapy and followed patients for 52 weeks. Both study arms showed significant improvements from baseline pain scores at 52 weeks, but there was no statistically significant difference between groups in terms of pain or function.[51]

Yoga

A review of 12 studies (including four RCTs) involving 589 patients with OA symptoms comparing a variety of yoga regimens to usual care found suggestions that pain, stiffness, and swelling were reduced. No effect on physical function was observed.[52]

A randomized trial of 131 older adults with lower extremity OA compared twice-weekly sessions of chair yoga vs. a health education program.[53] At 3-month follow-up, participants in the yoga group showed greater reductions in pain interferences (P=0.01) compared to control. During the intervention, patients in the yoga group had reduced pain on the WOMAC scale and improved gait speed compared to the control group, but the differences were not sustained at 3-month follow-up.[53]

Acupuncture

A Cochrane review of six randomized trials evaluating acupuncture in 413 patients with hip OA found conflicting evidence on its effects on pain and function.[54] In analysis of two trials with 105 patients comparing acupuncture to sham acupuncture there were no significant differences after 5-9 weeks in pain or function. One trial, however, that compared 13 weeks of acupuncture plus routine primary care vs. routine primary care alone in 137 patients found reduced pain and improved function. Two trials reported minor side effects with acupuncture, mostly bruising, bleeding, or pain at needle insertion site.

An unblinded trial randomized 221 adults with hip or knee OA to acupuncture, sham acupuncture, or mock electrical stimulation.[55] After five weeks of treatment no significant differences in mean improvements on a 0-100 pain scale were found for any comparisons.

Acupuncture trials can be particularly susceptible to placebo effects, as illustrated in a study comparing needle or laser acupuncture to no acupuncture or sham laser treatment in 282 patients with chronic knee pain (mean age 63). After 12 weeks of treatments, needle and laser acupuncture reduced self-reported knee pain more than no acupuncture (control) but not more than sham acupuncture, suggesting strong placebo effects. The benefits were not sustained at one year follow up.[31]

Massage

A review of seven randomized trials with 352 participants suggests that massage may be better than no treatment for reducing OA pain.[56]

The trials were diverse with respect to outcomes, massage techniques, and patient populations. Clinical effect sizes for pain were moderate with about a 20-point reduction in WOMAC scores from a baseline of 50-60 points. The functional benefits were less clear; some trials showed no benefit while others showed improvements in the 50-foot walk test.[56,57]

Self-management education programs

Small effects were noted in three meta-analyses of studies evaluating self-management education programs, though the benefits were not considered clinically important. Arthritis-specific programs included techniques to deal with problems associated with arthritis, appropriate exercises and medications, nutrition, and effective communication with healthcare providers and family.

Other non-drug interventions

TENS has been used for pain relief for decades, but studies evaluating effectiveness have shown mixed results. Data from four trials, including two RCTs, showed no statistical improvement in pain over placebo.[58]

CBT interventions typically address comorbid conditions, such as insomnia and depression. A systematic review, without meta-analysis, of four trials involving CBT or CBT-like pain coping skills trainings found inconsistent evidence for reduced pain at 12-month follow-up.[59]

A meta-analysis of 30 randomized trials evaluating mindfulness meditation for chronic pain (5 trials in patients with OA or RA) found a moderate improvement in pain (standardized mean difference 0.32, result limited by significant heterogeneity) compared to standard care, passive controls, or education/support groups.[34]

Pharmacologic options

NSAIDs

Given the inflammatory mechanism of OA, NSAIDs are the first-line pharmacologic option for managing OA-related chronic pain. In a network meta-analysis of 76 randomized trials evaluating oral celecoxib, ibuprofen, or naproxen vs. placebo in 58,451 patients with knee or hip OA, NSAIDs were associated with small-to-moderate effect sizes for improvements in pain and function, although results were not significant for naproxen at daily dose of 750 mg, or ibuprofen at daily dose of 1200 mg.[60]

Topical vs. Oral NSAIDs

Topical NSAIDs may be as effective as oral NSAIDs for OA pain. A randomized trial of 282 older patients with chronic knee pain comparing oral vs. topical ibuprofen found equivalent changes in the WOMAC OA index.[61] While side effects in the study did not vary between oral and topical NSAIDs, a small, statistically significant increase in serum creatinine was observed for oral NSAIDs. Generally, topical NSAIDs are considered safer due to a decreased systemic absorption. Topical NSAIDs may be recommended over oral NSAIDs for localized, single joint pain (e.g., knee OA).[62]

Acetaminophen

A 2019 Cochrane review of 10 randomized trials comparing acetaminophen vs. placebo in 3,541 patients with knee or hip OA found small, but not clinically important, reductions in pain and improvements in function with acetaminophen when used from between 3 weeks and 3 months.[63] These results should be interpreted cautiously, because daily acetaminophen doses of ~2,000 mg may not be effective over longer time frames (i.e., 3 months). The incidence of adverse events was similar between groups.[63] Generally, scheduled dosing is better than as-needed dosing for relief of chronic pain. The recommended starting dose of acetaminophen for elderly patients is 325 mg every 4 hours, with a maximum daily dose of 3000 mg.[62,64]

SNRIs

A meta-analysis of three trials of duloxetine for knee OA showed patients on duloxetine (60 or 120 mg daily) were 49% more likely to have a moderate pain response (≥30% reduction in pain intensity).[65] But the mean reduction in pain score with duloxetine compared to placebo on a 0-10 scale was only 0.88 points. Physical function improved modestly. No SNRIs are FDA approved to treat OA.

Anticonvulsants

A small randomized controlled trial (RCT) of 89 patients with knee OA suggests pregabalin may reduce pain and improve function compared to the NSAID meloxicam, but the combination of meloxicam with pregabalin was better than either alone.[66] The study lasted four weeks, and longer-term RCT data are still needed. Pregabalin is not FDA approved for OA.

Topical lidocaine

A 12-week RCT of 143 patients with knee OA found that a lidocaine 5% patch had similar effects on OA pain and function as celecoxib 200 mg daily.[67] However, lidocaine patches are not FDA approved for the treatment of OA, and more data are needed to support their use.

Other treatment options

Glucosamine and chondroitin, either alone or in combination, do not provide long-term benefit in OA, but a small number of clinical trials demonstrated that maximum effects were achieved at 3-6 months.[68] Topical capsaicin gel reduced pain 53% from baseline compared to a 27% reduction with placebo in one 12-week study. In a review of 2 studies, redness and burning sensation was reported by 44% and 46% of patients, respectively, randomized to capsaicin.[69]

A 2018 network meta-analysis of 28 trials, however found that topical capsaicin 0.025% four times daily and topical NSAIDs were equally effective for relieving pain in patients with knee or hand OA.[70]

Intra-articular injections

A number of injectable intra-articular agents are available to treat knee OA, with the two most-recently-approved being the synthetic corticosteroid triamcinolone acetonide extended release injection (Zilretta) and single-injection hyaluronic acid gel (Durolane). The evidence base for these treatments, however, is very weak, with effects frequently time-limited and study outcomes focused on cartilage and joint structure rather than pain and function.[68] A meta-analysis of 14 double-blind, sham-controlled trials with at least 60 patients in each trial found no clinically relevant differences between hyaluronic acid and sham injections.[71] Two randomized trials comparing single injection hyaluronic acid gel (Durolane) vs. placebo in a total of 564 patients with knee OA found no significant differences in pain, function, or joint stiffness at 6 weeks or 26 weeks.[72,73]

OA is a common reason for joint replacement surgery. For older patients with functionally disabling chronic pain unresponsive to other therapies, surgery may provide relief.

Low back pain

Low back pain (LBP) is one of the most common reasons for physician visits in the U.S., and about 25% of U.S. adults reported having LBP lasting at least a day in the past three months.[74] Imaging is of limited utility in diagnosing the cause of LBP because most patients have nonspecific findings, and asymptomatic patients often have abnormal findings. Magnetic resonance imaging (MRI) is recommended for red flag symptoms (for example, incontinence or saddle anesthesia), radicular symptoms, or risks for pathologic fracture.[75]

Current guidelines by the American College of Physicians recommend trying nonpharmacological options such as exercise, multidisciplinary rehabilitation, acupuncture, or yoga as first-line treatments for chronic low back pain, followed by pharmacologic treatment with an NSAID.[74] If the patient has an inadequate response, second-line options are a tricyclic antidepressant or duloxetine. Opioids, including tramadol, should be reserved for patients with pain unresponsive to all other treatments, with all of the caveats and cautions described previously[76], although some experts in pain medicine assert that opioids should never be used to treat nonstructural low back pain.[77]

Non-drug options

Exercise

In a review of 19 RCTs, exercise provided small reductions in pain compared to no exercise. Small, but not statistically significant, improvements in function were also observed.[35] Types and duration of exercise from RCTs included in the meta-analysis were not specified. Although physical therapy has a role in the management of acute low back pain, no RCTs of physical therapy were identified for chronic low back pain.

Weight loss

Only small, uncontrolled pilot studies suggest possible benefit from weight loss for patients with chronic low back pain.[78,79] After bariatric surgery, there was a 44% reduction in pain and a 26% improvement in function from a BMI reduction of 3 kg/m^2 (n=58).[79] Calorie restriction among obese patients suggests a reduction in pain and a significant improvement in function (n=46).[79] RCTs are needed to provide more conclusive evidence of benefit.

Tai Chi

Two trials (n=160 and n=320) found that tai chi modestly reduced pain versus wait list or no tai chi on a 0- to 10-point scale although these differences may not be clinically important.[80,81] The first trial randomized 160 adults with persistent non-specific low back pain to tai chi (18 sessions, 40 minutes each, over a 10-week period) vs. usual care.

In addition to reducing pain, tai chi reduced "bothersome" back symptoms and improved self-reported disability.[80]

Yoga

Several relatively high-quality RCTs suggest that yoga can modestly reduce chronic pain. A recent study, for example, found that people with chronic LBP who took weekly yoga classes for 12 weeks had less pain and greater physical function compared to those who just got information about how to deal with back pain.[82] The yoga in the study emphasized strengthening back and core muscles. In addition to reducing pain, those in the yoga group were more likely to have stopped taking pain relievers at one-year follow-up. A 2012 systematic review comparing yoga to standard care found moderate effect sizes for reductions in pain-related disability, with evidence that even short-term interventions might be effective.[83]

A 2017 Cochrane review of 9 RCTs involving 810 participants with chronic low back pain found small to moderate improvements in pain and function associated with yoga compared to no-exercise controls. For pain, a clinically meaningful reduction in pain score based on the RMDQ of 15 points was not achieved.[84] (A 2017 systematic review of 14 RCTs by the American College of Physicians came to similar conclusions.)[35]

Meditation

Mindfulness meditation elicits the relaxation response and can promote pain relief. A randomized trial of 342 adults with LBP found that participating in 8 weekly training sessions in mindfulness meditation was associated with significantly higher levels of function and reduced pain compared to usual care (61% vs. 44%, p=0.04).[85] The neural correlates of the analgesic effects of mindfulness meditation were explored in a trial at Wake Forest University in which 76 healthy volunteers were taught mindfulness meditation and then monitored by MRI while a pain-inducing heat device was applied to their leg for six minutes.[86] Meditation reduced pain unpleasantness by more than half (57%) and pain intensity by 40%.[86]

Acupuncture

A 2017 systematic review of four trials evaluating acupuncture vs. sham acupuncture in patients with chronic LBP found modest improvements in pain, but no improvements in function.[35] A meta-analysis of 4 trials comparing acupuncture to no acupuncture found larger effect sizes, but the quality of the evidence is lower due to the large placebo effects known to manifest in acupuncture studies without a sham comparison.[35]

Massage

A 2015 Cochrane review of 25 RCTs compared massage vs. inactive (e.g., sham treatment or waitlist) or active (e.g., TNES, acupuncture, traction, physical therapy) controls in 3,096 adults with LBP.[87]Massage compared to sham massage or no treatment showed moderate reductions in pain and disability in the short term (<6 months), but not in the long-term. In studies comparing massage to active therapies, massage resulted in greater pain reduction both in the short term, and in the long term, but no difference in disability reduction was observed.[87]

TENS

Existing clinical studies indicate that TENS has no beneficial effect on pain or function versus sham or placebo.[74,87,88]

Cognitive and behavioral/mindfulness therapies

A meta-analysis of five RCTs evaluating CBT found no difference in function but a moderate reduction in pain intensity compared to waitlist controls.[35]

A more recent trial randomized 342 patients with chronic LBP to CBT, mindfulness-based stress reduction, or usual care. Both the CBT and mindfulness intervention consisted of eight weekly two-hour classes. Both mindfulness and CBT were associated with greater improvements in pain and function compared to usual care at 26 weeks (with benefit persisting at 52 week follow-up vs. usual care) with no statistically significant differences between CBT and mindfulness groups.[87]

Drug options

Acetaminophen

Two small trials have evaluated acetaminophen in patients with chronic LBP. A trial conducted in the early 1980s randomized 30 patients to 1000 mg acetaminophen four times daily vs. the NSAID diflunisal 500 mg twice daily for 4 weeks.[89] Another trial randomized 45 patients with either acute or chronic LBP to 500 mg acetaminophen vs. amitriptyline 37.5 mg four times daily.[90] No significant differences were found between acetaminophen and diflunisal in pain relief or reduced disability, and acetaminophen was less effective than amitriptyline for reducing pain.[91]

No trials have compared acetaminophen vs. placebo for chronic pain, however a 2016 Cochrane review of three trials with 1,825 patients with acute LBP found high-quality evidence that acetaminophen was no more effective than placebo for pain, disability, function, and quality of life.[92]

NSAIDs

A review of six RCTs for the American College of Physicians showed that oral NSAIDs are more effective than placebo regarding pain intensity, with a small reduction in pain at 12 weeks.[93] No differences in efficacy between different NSAIDs, including non-selective NSAIDs vs. selective COX2 inhibitors, were identified. No trials were identified evaluating the efficacy of topical NSAIDs on chronic LBP.

Antidepressants

Duloxetine

An analysis of three moderate-quality RCTs found small improvements in pain and function with duloxetine vs. placebo at 12 to 13 weeks.[94] One of the studies involved 401 patients randomized to duloxetine 60 mg daily or placebo. Compared with placebo, duloxetine-treated patients reported a significantly greater reduction ($P \leq 0.001$) in pain on the Brief Pain Inventory (BPI).[95] A 2017 systematic review found that SSRIs and TCAs were not significantly better than placebo for reducing pain or improving function in patients with chronic LBP.[94]

Other therapies

Other drug options such as gabapentin, pregabalin, topical lidocaine, and muscle relaxants have little or no data for use in managing chronic low back pain. For the anticonvulsants pregabalin and gabapentin, a small number of low-quality RCTs failed to show a reduction in pain or improvement in function compared to placebo.[96] No data exist to support the use of topical lidocaine for low back pain without a neuropathic component. While widely prescribed, use of skeletal muscle relaxants for chronic LBP is not supported by evidence.[96]

Additional interventions

Epidural steroid injections

Lumbar epidural steroid injections under fluoroscopic guidance are commonly used to treat low back pain.[97]. The strength of the evidence varies according to the type and cause of the pain and the type of injection.[98] For example, the evidence for the efficacy of treatment of disc herniation with interlaminar lumbar epidural and transformaminal lumbar epidural injections is strong.. In contrast, for spinal stenosis, the evidence is moderate-to-fair for interlaminar lumbar epidural injections and fair-to-limited for intraforaminal lumbar epidural injections.[98]

Spinal fusion

An RCT of 349 patients with chronic low back pain comparing spinal fusion surgery against intensive rehabilitation showed small functional benefits in favor of surgery.

Those assigned to surgery had more complications (dural tears, excessive bleeding, repeat surgery).[99]

Diabetic neuropathy

Diabetic neuropathy most commonly affects the distal extremities in a symmetric fashion causing numbness, tingling, pain, loss of vibratory sensation, and altered proprioception. Improved glucose control may reduce the risk of acquiring diabetic neuropathy and slow its progression,[100] and in those who have neuropathy, pain management may improve quality of life.[101]

Current American Diabetes Association guidelines suggest initial management with pregabalin, duloxetine, or gabapentin.[100] Second-line options include TCAs (use cautiously in older adults), venlafaxine, or carbamazepine. Opioids, and particularly tapentadol, are not recommended to treat neuropathy due to their risk for addiction and limited evidence for efficacy.[100] Tapentadol is FDA-approved to treat diabetic neuropathy, but the approval was based on two trials that used a design enriched for patients who responded to tapentadol, therefore the results are not generalizable.[100] Because tapentadol incurs similar risks of addiction and safety compared to typical opioids, it's use is generally not recommended as first- or second-line therapy for neuropathic pain.[100]

Non-drug options

Movement-based options

A small RCT of 39 Korean patients with type 2 diabetes and neuropathy found tai chi improved quality of life on five domains, including pain, physical functioning, social functioning, vitality and a mental component score, compared with usual care, but there was no significant difference in neuropathy scores.[102]

Acupuncture and massage

Small studies suggest a possible effect of acupuncture and massage on pain and function. A pilot study of 46 patients found overall symptom improvement from baseline with acupuncture in 77% of patients with 67% discontinuing medication. However, the study didn't have a control group nor did it specifically identify pain as an endpoint.[103] A 4-week trial involving 46 patients who received aromatherapy and massage had reduced pain and improved quality of life compared to usual care.[104] A 2014 trial randomized 45 patients to acupuncture vs. sham acupuncture for 10 weeks and found no significant differences in pain outcomes.[105] Further studies are required to provide a more clear understanding of the role of acupuncture and massage in managing pain in diabetic neuropathy.

TENS

A meta-analysis of three trials comparing TENS vs. placebo in 78 patients with diabetic neuropathy found reduced pain severity at four weeks and six weeks but not at 12 weeks.[106] An analysis by the Agency for Healthcare Research and Quality (AHRQ), however, did not find significant or compelling evidence to suggest TENS was more effective than placebo for diabetic neuropathy.[107]

Cognitive and behavioral interventions

Little data support cognitive and behavioral interventions for patients with diabetic neuropathy. A small trial of 20 patients receiving CBT showed a greater decrease in pain scores at 4-month follow-up, compared with usual care.[108] A small study of 20 patients found no difference with mindfulness meditation versus placebo on pain or quality of life.[109]

Pharmacologic options

Pregabalin, duloxetine, and tapentadol are FDA-approved for the treatment of neuropathic pain in diabetes. Other medications, such as gabapentin, oxcarbazepine, TCAs, topical lidocaine or capsaicin have been used off-label with varying degrees of success.

Acetaminophen and NSAIDs

No published trials have evaluated the use of acetaminophen alone or NSAIDs, either oral or topical, for diabetic neuropathy.

SNRIs

Both duloxetine and venlafaxine have been shown to reduce pain related to diabetic neuropathy compared to placebo. A network meta-analysis found relatively large effect sizes for pain reduction for duloxetine vs. placebo, and venlafaxine vs. placebo.[110] A 12-week study randomized 457 patients with painful diabetic neuropathy to three duloxetine groups (20 mg/day, 60 mg/day, and 120 mg/day) or placebo.[111] At follow-up, the mean daily pain severity score in the placebo group had dropped 1.91 points (on a 0-10 scale), with greater reductions in the three duloxetine groups: 2.36 points in the 20 mg group (not significant vs. placebo), 2.89 points in the 60 mg group ($P<0.001$ vs. placebo), and 3.24 points in the 120 mg group ($P<0.001$ vs. placebo).[111]

TCAs

TCAs studied for diabetic neuropathy include amitriptyline, imipramine, and desipramine. A meta-analysis of five RCTs found a modest effect size for pain reduction for amitriptyline.[110] Adverse effects with TCAs included somnolence and dizziness, which may be particularly important in older patients.

Anticonvulsants

The American Diabetes Association recommends using pregabalin or gabapentin, noting that gabapentin may be less expensive than pregabalin, although it is not FDA-approved for the indication of neuropathic pain.[101] Other anticonvulsants (e.g., carbamazepine, topiramate, valproic acid, lacosamide, lamotrigine) lack clear evidence of benefit but have documented harms.[112]

Gabapentin is a commonly prescribed off-label to treat diabetic neuropathy. Based on a review of five RCTs with 766 patients, gabapentin had a large overall effect on pain severity, however, the result was not statistically significant. A 2019 Cochrane review of 20 randomized trials found that pregabalin 300 mg/day modestly reduced pain intensity.[113] Rates of fatigue and dizziness were significantly higher with pregabalin.

Topical lidocaine

Although lidocaine patches are FDA approved for post-herpetic neuralgia, no RCTs of patches have been conducted in diabetic neuropathy. One open-label, 4-week trial of 300 patients with painful diabetic polyneuropathy or post-herpetic neuralgia evaluated 5% lidocaine medicated plaster vs. pregabalin. In post-herpetic neuralgia more patients responded to 5% lidocaine medicated plaster treatment than to pregabalin (62.2% vs. 46.5% [no P value reported]), while response was comparable for patients with painful diabetic polyneuropathy (in the per-protocol set): 66.7% vs. 69.1% (no P value reported).[114]

Cannabinoids for diabetic neuropathy

Weak evidence suggests that medical marijuana and cannabinoids may reduce pain related to diabetic neuropathy.

A Cochrane review of 16 randomized trials published through November 2017 comparing cannabis-based treatments to placebo in 1,750 adults with chronic neuropathic pain found slight reductions in pain intensity and increased numbers of patients achieving 50% or greater reductions in pain (21% vs. 17%).[43] The results, however, are limited by poor trial quality (only 2 trials were judged high-quality) and heterogeneity in treatments (10 trials evaluated an oromucosal spray containing THC or CBD, 2 trials evaluated a synthetic THC, 2 trials evaluated plant-derived THC, and 2 trials evaluated inhaled herbal cannabis). There were no significant differences in the rates of serious adverse events, but more people reported sleepiness, dizziness, or confusion in the cannabis groups.

A study of high and low potency cannabis cigarettes (7% or 3.5% THC) in 44 patients with neuropathic pain showed reduced pain scores in both cannabis cigarette groups vs. placebo cigarettes ($P<0.01$) with no significant differences between the two doses of cannabis.[115]

A 2012 study evaluated the oral cannabinoid nabilone (Cesamet) used as adjuvant to regular pain medications in 37 patients with diabetic neuropathy.[116] At 4 weeks, 70% of patients had at least a 30% reduction in pain. An open-label 5-week extension treatment period found a THC dose of 3 mg (range 1-4 mg) effective for continued pain reduction.[117]

A small randomized cross-over trial in 16 patients with diabetic peripheral neuropathy compared the analgesic effects of three doses of inhaled cannabis (1% THC, 4% THC, or 7% THC) vs. placebo with pain sensitivity assessed after 4 hours.[117] Mean spontaneous pain scores (using 10-point scale) were modestly lower with all THC doses vs. placebo (-0.44 points with low dose, -0.42 points with medium dose, and -1.2 points with high dose, $P<0.05$ for all comparisons). Mean pain scores with evoked pain were only significant with high-dose THC ($P<0.001$). The percentage of patients with 30% or greater reductions in spontaneous pain were higher in the medium and high dose groups, but the differences with placebo did not reach statistical significance.

Another trial randomized 30 patients with chronic painful diabetic neuropathy to a sublingual spray containing 27 mg/mL THC and 25 mg/mL CBD (Sativex) vs. placebo spray, both administered four times daily for 12 weeks.[118] No significant differences were reported for change in pain scores from baseline for superficial, deep, or muscular pain, or in the percentages of patients reporting 30% or greater reductions in pain.

An un-published clinical trial that randomized 297 patients with diabetic neuropathy to Sativex oromucosal spray (maximum daily dose of 65 mg THC and 60 mg CBD) vs. placebo for 14 weeks found no significant differences in pain intensity between groups.[119]

None of the reviewed studies evaluated long-term efficacy and safety of cannabinoid exposure.

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

Other drug options

Evidence for the SSRIs paroxetine and citalopram is inconsistent and insufficient to recommend their use in managing pain in diabetic neuropathy. However, these drugs may be effective if patients have coexisting pain and depression.[120] Earlier studies showed that treatment with topical capsaicin was beneficial for relieving pain in patients with diabetic neuropathy.[121,122] However, a 2017 meta-analysis of 5 randomized trials found that 0.075% capsaicin cream was no more effective than placebo (SMD -0.46; 95% CI: -0.95 to 0.03).[123]

Fibromyalgia

The European League Against Rheumatism (EULAR) guidelines for managing fibromyalgia-related pain recommend beginning with non-drug approaches (exercise, CBT, acupuncture, yoga, tai chi, and mindfulness) and then advancing to pharmacologic options (low dose amitriptyline, duloxetine or milnacipran, pregabalin). Most recommendations were considered weak, with the exception of exercise.[124] In the elderly, duloxetine or milnacipran and pregabalin or gabapentin may be the more favorable pharmacologic options.

Non-drug options

Movement-based options

Exercise training is often recommended for patients with fibromyalgia,[125] not only for potential pain reductions, but for the other known physiologic benefits associated with exercise. The effects of exercise in fibromyalgia have been assessed in more than 30 trials, with the overall quality rated as moderate.[124] Some reviews have concluded that the strongest evidence was in support of aerobic exercise,[126] which is the current recommendation by the American College of Rheumatology. However, resistance training can be of benefit as well.[127] A 2017 Cochrane review of eight RCTs (n=456) comparing aerobic exercise training vs. no exercise or another type of intervention found small improvements (relative to comparators) in pain intensity (relative improvement 18%), stiffness (11.4%) and physical function (22%).[128]

Case Study 3

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

Cassandra, 26, was diagnosed with type 1 diabetes at the age of 14. She presents with persistent burning pain in her lower extremities as well as numbness in her hands that make her work as a dental hygienist difficult. Recently, her family has noted that she seems to be stumbling at times. Cassandra has no history of diabetic retinopathy or nephropathy. She also denies resting tachycardia, orthostatic lightheadedness, early satiety, early morning nausea, changes in bowel habits, or postprandial sweating. She has a history of depression, which was treated with counseling and medication. She also notes menstrual irregularity, dysmenorrhea, and premenstrual emotional lability. She had been treated with oral contraceptives in the past, but had discontinued these 6–8 months ago. She had been prescribed a selective serotonin reuptake inhibitor (SSRI) for her pain symptoms as well as her depression, but she reports no relief of pain after 2 months. Her glycemic control has never been optimal despite a multiple-dose insulin program. Her hemoglobin A1C levels have typically been in the 8–9% range. Exam revealed a moderately overweight (BMI 27 kg/m^2) woman with a blood pressure of 138/85 mmHg with no orthostatic change and a resting pulse of 72. Laboratory testing revealed an A1C of 8.2%; an albumin-to-creatinine ratio of 25 µg/mg; and normal serum creatinine, complete blood count, total protein, sedimentation rate, and thyroid stimulating hormone.

1. **What kinds of pharmacologic treatment options might you suggest for Cassandra?**_____

2. **Are there any non-pharmacologic approaches that might help relieve her symptoms?**_____

3. **What kinds of functional benchmarks might you set up to allow you and Cassandra to monitor progress, both in terms of pain and glycemic control?**_____

A separate Cochrane review of 5 studies with 219 women with fibromyalgia found that moderate-to-high intensity resistance training improves function and reduces pain and tenderness vs. control, and that eight weeks of aerobic exercise was superior to moderate-intensity resistance exercise for reducing pain, although the quality of the evidence was rated as low.[129]

Tai chi may help reduce pain and other symptoms related to fibromyalgia. One trial randomized 66 patients with fibromyalgia to tai chi twice weekly for 12 weeks vs. wellness education and stretching exercises. Tai chi improved scores on the Fibromyalgia Impact Questionnaire (FIQ) that assessed pain, physical functioning, fatigue, morning stiffness, and on the Medical Outcomes Study 36 Item Short Form Health Survey (SF-36) both at the end of the intervention (12 weeks) and at 24-week follow-up. At 12 weeks, mean between group difference was -18.4 FIQ points (P<0.001).[130]

Acupuncture, massage, and TENS

One in five patients with fibromyalgia try acupuncture within two years of diagnosis,[131] and low-quality evidence suggests that acupuncture may be associated with reduced fibromyalgia-related pain. A 2013 Cochrane review of 9 RCTs with 395 adults with fibromyalgia found reduced pain and stiffness at 1 month with electro-acupuncture compared to either placebo or sham acupuncture, but there were no significant differences in pain, fatigue, or sleep comparing manual acupuncture to placebo or sham acupuncture (4 trials, 182 adults).[131]

Based on two small trials, myofascial massage may improve pain over placebo.[132] Although data recommending other forms of massage for reducing pain are limited, most styles of massage therapy consistently improved quality of life for patients with fibromyalgia.

Six RCTs failed to show that TENS reduced pain in fibromyalgia.[133]

Cognitive and behavioral interventions

A Cochrane Review of 18 RCTs showed a small benefit from traditional CBT programs on pain and function.[134] Controls included waitlist controls, active controls, or treatment as usual, and the overall quality of evidence was rated as low.

In seven RCTs of mindfulness medication, no reduction in pain was observed. Methods were varied and incorporated different components of mindfulness-based stress relief, CBT, and yoga.[34] In two RCT, self-management education did not improve pain or disability, as compared to controls.[34]

Drug options

The FDA has approved three drugs for the treatment of fibromyalgia: duloxetine, milnacipran and pregabalin. Other options used off-label include gabapentin, amitriptyline, and SSRIs.

Acetaminophen and NSAIDs

No data support the efficacy of acetaminophen or NSAIDs for treating pain in patients with fibromyalgia,[135] although they may be useful to treat pain triggers of fibromyalgia.[125]

SNRIs

Duloxetine

A 2014 Cochrane review included six RCTs randomizing 2249 adults with fibromyalgia to duloxetine vs. placebo with 12-week to 6-month follow-up.[136] At 12 weeks, duloxetine was superior to placebo for pain reduction, with superiority also shown at 28 weeks.

Milnacipran

In a Cochrane meta-analysis of three RCTs evaluating milnacipran 100 mg daily vs. placebo in 1,925 patients with fibromyalgia, milnacipran was more effective for inducing at least 30% reduction in pain.[137] A similar effect on pain relief was noted with milnacipran 200 mg daily.

An updated Cochrane review identified additional 7 trials of duloxetine and 9 of milnacipran.[138] The updated analysis did not change findings from previous reviews: both drugs were better than placebo in reducing pain by at least 30%. Both drugs were also found to improve health-related quality of life, although more SNRI patients dropped out of trials due to adverse events as compared to placebo.

Antidepressants

A meta-analysis of nine trials of the TCA amitriptyline found a small improvement in pain.[139] A Cochrane review of seven RCTs found a small difference in patients who reported a 30% pain reduction between SSRIs (33%) and placebo (23%). SSRIs included in the review included citalopram, fluoxetine, and paroxetine.[140] These data are insufficient to recommend SSRIs for the treatment of pain alone in patients with fibromyalgia.

Anticonvulsants

Pregabalin

A meta-analysis of five RCTs found pregabalin, overall, had a small effect on pain. Low doses (150 mg per day) were no different than placebo, but doses of 300 mg daily or greater were more likely to result in a 50% reduction in pain than placebo.[141]

A crossover randomized trial with 41 patients with fibromyalgia found that combining pregabalin with duloxetine more effectively reduced pain (68% reporting at least moderate global pain relief) vs. either pregabalin (39%) or duloxetine (42%) alone (P<0.05 for both comparisons with combination).[142]

Gabapentin

Evidence supporting the use of gabapentin for fibromyalgia is limited. A Cochrane review of RCTs lasting 8 weeks or longer (searched through May 2016) identified two trials, one of which was only a conference abstract. The other trial randomized 150 patients with fibromyalgia to gabapentin 1200-2400 mg/day vs. placebo for 12 weeks.[143] Gabapentin was associated with a small reduction in pain (mean difference between groups at 12 weeks: -0.92 points on 0-10 point BPI scale; 95% CI: -1.75 to -0.71 points) but this difference may not be clinically important.

Cannabinoids

Two small trials have evaluated the oral cannabinoid nabilone (a synthetic form of THC) in patients with fibromyalgia. One trial randomized 46 patients to nabilone 0.5 mg to 1 mg twice daily for 4 weeks vs. placebo and found significant reductions in pain and improvements in anxiety on the Fibromyalgia Impact Questionnaire (P<0.05 for both outcomes).[144] Another trial randomized 31 patients with fibromyalgia and chronic insomnia to nabilone 0.5 mg to 1 mg at bedtime vs. amitriptyline 10-20 mg at bedtime for 4 weeks.[145] Although nabilone was associated with improved sleep quality, no significant effects were reported for pain, mood, or quality of life.

Conclusions

This learning activity has reviewed an evidence-based path toward increasing use of non-opioid therapies for treating acute and chronic pain conditions, emphasizing holistic assessment, individualized treatment planning, and multi-modal therapeutic approaches.

Pain treatment plans should be grounded on realistic functional goals. The level of pain management needed to reach those goals should be determined using a shared decision-making approach. In general, non-drug options (which can be as effective as drug options) should be tried first. When drug options are considered, it is important to maximize non-opioid options before trying opioids.

Since much acute pain is self-limiting and remits with healing (typically within a month), helping patients frame expectations about acute pain and pain relief can provide reassurance and reduce fear, worry, and distress. Multimodal approaches should be used to manage acute pain, combining non-drug as well as appropriate drug-based options.

References

1. Jamison RN, Sheehan KA, Scanlan E, Matthews M, Ross EL. Beliefs and attitudes about opioid prescribing and chronic pain management: survey of primary care providers. J Opioid Manag. 2014;10(6):375-382.
2. Wilson HD, Dansie EJ, Kim MS, Moskovitz BL, Chow W, Turk DC. Clinicians' attitudes and beliefs about opioids survey (CAOS): instrument development and results of a national physician survey. J Pain. 2013;14(6):613-627.
3. Brummett CM, Waljee JF, Goesling J, et al. New Persistent Opioid Use After Minor and Major Surgical Procedures in US Adults. JAMA Surg. 2017;152(6):e170504.
4. Calcaterra SL, Yamashita TE, Min SJ, Keniston A, Frank JW, Binswanger IA. Opioid Prescribing at Hospital Discharge Contributes to Chronic Opioid Use. Journal of general internal medicine. 2016;31(5):478-485.
5. Bateman BT, Franklin JM, Bykov K, et al. Persistent opioid use following cesarean delivery: patterns and predictors among opioid-naive women. Am J Obstet Gynecol. 2016;215(3):353 e351-353 e318.
6. Johnson SP, Chung KC, Zhong L, et al. Risk of Prolonged Opioid Use Among Opioid-Naive Patients Following Common Hand Surgery Procedures. The Journal of hand surgery. 2016;41(10):947-957 e943.
7. Centers for Disease Control & Prevention. Opioid overdose: Understanding the Epidemic. https://www.cdc.gov/drugoverdose/images/3-waves-2019.PNG. Published 2021. Accessed June 10, 2021.
8. Busse JW, Wang L, Kamaleldin M, et al. Opioids for Chronic Noncancer Pain: A Systematic Review and Meta-analysis. Jama. 2018;320(23):2448-2460.
9. Krebs EE, Gravely A, Nugent S, et al. Effect of Opioid vs Nonopioid Medications on Pain-Related Function in Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain: The SPACE Randomized Clinical Trial. Jama. 2018;319(9):872-882.
10. Fishman SM. Responsible Opioid Prescribing: A Clinician's Guide, 2nd Ed. Washington, DC: Waterford Life Sciences; 2012.
11. Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. British journal of anaesthesia. 1997;78(5):606-617.
12. Pengel LH, Herbert RD, Maher CG, Refshauge KM. Acute low back pain: systematic review of its prognosis. BMJ. 2003;327(7410):323.
13. Traeger AC, Hubscher M, Henschke N, Moseley GL, Lee H, McAuley JH. Effect of Primary Care-Based Education on Reassurance in Patients With Acute Low Back Pain: Systematic Review and Meta-analysis. JAMA internal medicine. 2015;175(5):733-743.
14. Brat GA, Agniel D, Beam A, et al. Postsurgical prescriptions for opioid naive patients and association with overdose and misuse: retrospective cohort study. BMJ. 2018;360:j5790.
15. Hall MJ, Schwartzman A, Zhang J, Liu X. Ambulatory Surgery Data From Hospitals and Ambulatory Surgery Centers: United States, 2010. Natl Health Stat Report. 2017(102):1-15.
16. American Pain Society. Management of acute pain and chronic noncancer pain. http://americanpainsociety.org/education/enduring-materials. Accessed October 29 2018.
17. Frogner BK, Harwood K, Andrilla CHA, Schwartz M, Pines JM. Physical Therapy as the First Point of Care to Treat Low Back Pain: An Instrumental Variables Approach to Estimate Impact on Opioid Prescription, Health Care Utilization, and Costs. Health Serv Res. 2018;53(6):4629-4646.
18. Centers for Disease Control & Prevention. Module 2: Treating Pain Without Opioids. Course number WB2859. https://www.cdc.gov/drugoverdose/training/nonopioid. Published 2018. Accessed February 10, 2019.
19. Food and Drug Administration. Don't double up on acetaminophen. https://www.fda.gov/consumers/consumer-updates/dont-double-acetaminophen. Published 2018. Accessed July 12 2019.
20. Paice JA, Ferrans CE, Lashley FR, Shott S, Vizgirda V, Pitrak D. Topical capsaicin in the management of HIV-associated peripheral neuropathy. J Pain Symptom Manage. 2000;19(1):45-52.
21. Low PA, Opfer-Gehrking TL, Dyck PJ, Litchy WJ, O'Brien PC. Double-blind, placebo-controlled study of the application of capsaicin cream in chronic distal painful polyneuropathy. Pain. 1995;62(2):163-168.
22. Macintyre PE, Ready LB. Acute Pain Management: A Practical Guide, 2nd Ed. London: Saunders; 2003.
23. Goodman CW, Brett AS. Gabapentin and Pregabalin for Pain - Is Increased Prescribing a Cause for Concern? N Engl J Med. 2017;377(5):411-414.
24. Mathieson S, Maher CG, McLachlan AJ, et al. Trial of Pregabalin for Acute and Chronic Sciatica. N Engl J Med. 2017;376(12):1111-1120.
25. Schwenk ES, Viscusi ER, Buvanendran A, et al. Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Acute Pain Management From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Regional anesthesia and pain medicine. 2018;43(5):456-466.
26. Food and Drug Administration. Opioid analgesic risk evaluation and mitigation strategy (REMS). https://www.fda.gov/drugs/information-drug-class/opioid-analgesic-risk-evaluation-and-mitigation-strategy-rems. Published 2018. Accessed June 10 2019.
27. Fransen M, McConnell S, Harmer AR, Van der Esch M, Simic M, Bennell KL. Exercise for osteoarthritis of the knee. The Cochrane database of systematic reviews. 2015;9(1).
28. Kang JW, Lee MS, Posadzki P, Ernst E. T'ai chi for the treatment of osteoarthritis: a systematic review and meta-analysis. BMJ Open. 2011;1(1):2010-000035.
29. Sherman KJ, Cherkin DC, Wellman RD, et al. A randomized trial comparing yoga, stretching, and a self-care book for chronic low back pain. Archives of internal medicine. 2011;171(22):2019-2026.
30. Messier SP, Mihalko SL, Legault C, et al. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: the IDEA randomized clinical trial. Jama. 2013;310(12):1263-1273.
31. Hinman RS, McCrory P, Pirotta M, et al. Acupuncture for chronic knee pain: a randomized clinical trial. Jama. 2014;312(13):1313-1322.
32. Reid MC, Eccleston C, Pillemer K. Management of chronic pain in older adults. Bmj. 2015;13(350).
33. Morley S, Eccleston C, Williams A. Systematic review and meta-analysis of randomized controlled trials of cognitive behaviour therapy and behaviour therapy for chronic pain in adults, excluding headache. Pain. 1999;80(1-2):1-13.
34. Hilton L, Hempel S, Ewing BA, et al. Mindfulness Meditation for Chronic Pain: Systematic Review and Meta-analysis. Ann Behav Med. 2017;51(2):199-213.
35. Chou R, Deyo R, Friedly J, et al. Nonpharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline. Annals of internal medicine. 2017;166(7):493-505.

36. Bicket MC, Horowitz JM, Benzon HT, Cohen SP. Epidural injections in prevention of surgery for spinal pain: systematic review and meta-analysis of randomized controlled trials. Spine J. 2015;15(2):348-362.
37. Gupta A, Huettner DP, Dukewich M. Comparative Effectiveness Review of Cooled Versus Pulsed Radiofrequency Ablation for the Treatment of Knee Osteoarthritis: A Systematic Review. Pain physician. 2017;20(3):155-171.
38. Deer TR, Mekhail N, Provenzano D, et al. The appropriate use of neurostimulation of the spinal cord and peripheral nervous system for the treatment of chronic pain and ischemic diseases: the Neuromodulation Appropriateness Consensus Committee. Neuromodulation. 2014;17(6):515-550; discussion 550.
39. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain. 2009;10(2):113-130.
40. DISA Global Solutions. Map of Marijuana legality by state. https://disa.com/map-of-marijuana-legality-by-state. Accessed May 18, 2020.
41. Rahn EJ, Zvonok AM, Thakur GA, Khanolkar AD, Makriyannis A, Hohmann AG. Selective activation of cannabinoid CB2 receptors suppresses neuropathic nociception induced by treatment with the chemotherapeutic agent paclitaxel in rats. J Pharmacol Exp Ther. 2008;327(2):584-591.
42. National Academies of Science. In: The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. Washington (DC) 2017.
43. Mucke M, Phillips T, Radbruch L, Petzke F, Hauser W. Cannabis-based medicines for chronic neuropathic pain in adults. The Cochrane database of systematic reviews. 2018;3:CD012182.
44. Stockings E, Campbell G, Hall WD, et al. Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies. Pain. 2018;159(10):1932-1954.
45. Hill KP. Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems: A Clinical Review. Jama. 2015;313(24):2474-2483.
46. Narang S, Gibson D, Wasan AD, et al. Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. J Pain. 2008;9(3):254-264.
47. Walitt B, Klose P, Fitzcharles MA, Phillips T, Hauser W. Cannabinoids for fibromyalgia. The Cochrane database of systematic reviews. 2016;18(7).
48. Hurley M, Dickson K, Hallett R, et al. Exercise interventions and patient beliefs for people with hip, knee or hip and knee osteoarthritis: a mixed methods review. The Cochrane database of systematic reviews. 2018;4:CD010842.
49. Chen H, Zheng X, Huang H, Liu C, Wan Q, Shang S. The effects of a home-based exercise intervention on elderly patients with knee osteoarthritis: a quasi-experimental study. BMC Musculoskelet Disord. 2019;20(1):160.
50. Hall A, Copsey B, Richmond H, et al. Effectiveness of Tai Chi for Chronic Musculoskeletal Pain Conditions: Updated Systematic Review and Meta-Analysis. Phys Ther. 2017;97(2):227-238.
51. Wang C, Schmid CH, Iversen MD, et al. Comparative Effectiveness of Tai Chi Versus Physical Therapy for Knee Osteoarthritis: A Randomized Trial. Annals of internal medicine. 2016;165(2):77-86.
52. Cheung C, Park J, Wyman JF. Effects of Yoga on Symptoms, Physical Function, and Psychosocial Outcomes in Adults with Osteoarthritis: A Focused Review. Am J Phys Med Rehabil. 2016;95(2):139-151.
53. Park J, McCaffrey R, Newman D, Liehr P, Ouslander JG. A Pilot Randomized Controlled Trial of the Effects of Chair Yoga on Pain and Physical Function Among Community-Dwelling Older Adults With Lower Extremity Osteoarthritis. J Am Geriatr Soc. 2017;65(3):592-597.
54. Manheimer E, Cheng K, Wieland LS, et al. Acupuncture for hip osteoarthritis. The Cochrane database of systematic reviews. 2018;5:CD013010.
55. White P, Bishop FL, Prescott P, Scott C, Little P, Lewith G. Practice, practitioner, or placebo? A multifactorial, mixed-methods randomized controlled trial of acupuncture. Pain. 2012;153(2):455-462.
56. Nelson NL, Churilla JR. Massage Therapy for Pain and Function in Patients With Arthritis: A Systematic Review of Randomized Controlled Trials. Am J Phys Med Rehabil. 2017;96(9):665-672.
57. Perlman AI, Sabina A, Williams AL, Njike VY, Katz DL. Massage therapy for osteoarthritis of the knee: a randomized controlled trial. Archives of internal medicine. 2006;166(22):2533-2538.
58. Canadian Agency for Drugs and Technologies in Health. Home Transcutaneous Electrical Nerve Stimulation for Chronic Pain: A review of the clinical effectiveness. Ottawa Ontario 2016.
59. Ismail A, Moore C, Alshishani N, Yaseen K, Alshehri MA. Cognitive behavioural therapy and pain coping skills training for osteoarthritis knee pain management: a systematic review. J Phys Ther Sci. 2017;29(12):2228-2235.
60. da Costa BR, Reichenbach S, Keller N, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. Lancet. 2017;390(10090):e21-e33.
61. Underwood M, Ashby D, Cross P, et al. Advice to use topical or oral ibuprofen for chronic knee pain in older people: randomised controlled trial and patient preference study. BMJ. 2008;336(7636):138-142.
62. Makris UE, Abrams RC, Gurland B, Reid MC. Management of persistent pain in the older patient: a clinical review. Jama. 2014;312(8):825-836.
63. Leopoldino AO, Machado GC, Ferreira PH, et al. Paracetamol versus placebo for knee and hip osteoarthritis. The Cochrane database of systematic reviews. 2019;2:CD013273.
64. Zhang W, Jones A, Doherty M. Does paracetamol (acetaminophen) reduce the pain of osteoarthritis? A meta-analysis of randomised controlled trials. Ann Rheum Dis. 2004;63(8):901-907.
65. Wang ZY, Shi SY, Li SJ, et al. Efficacy and Safety of Duloxetine on Osteoarthritis Knee Pain: A Meta-Analysis of Randomized Controlled Trials. Pain medicine. 2015;16(7):1373-1385.
66. Ohtori S, Inoue G, Orita S, et al. Efficacy of combination of meloxicam and pregabalin for pain in knee osteoarthritis. Yonsei Med J. 2013;54(5):1253-1258.
67. Kivitz A, Fairfax M, Sheldon EA, et al. Comparison of the effectiveness and tolerability of lidocaine patch 5% versus celecoxib for osteoarthritis-related knee pain: post hoc analysis of a 12 week, prospective, randomized, active-controlled, open-label, parallel-group trial in adults. Clinical therapeutics. 2008;30(12):2366-2377.
68. AHRQ. Treatment of osteoarthritis of the knee: an update review #19. Rockville MD 2017.
69. Guedes V, Castro JP, Brito I. Topical capsaicin for pain in osteoarthritis: A literature review. Reumatol Clin. 2016;26(16):30089-30084.
70. Persson MSM, Stocks J, Walsh DA, Doherty M, Zhang W. The relative efficacy of topical non-steroidal anti-inflammatory drugs and capsaicin in osteoarthritis: a network meta-analysis of randomised controlled trials. Osteoarthritis Cartilage. 2018;26(12):1575-1582.
71. Jevsevar D, Donnelly P, Brown GA, Cummins DS. Viscosupplementation for Osteoarthritis of the Knee: A Systematic Review of the Evidence. J Bone Joint Surg Am. 2015;97(24):2047-2060.

72. Altman RD, Akermark C, Beaulieu AD, Schnitzer T, Durolane International Study G. Efficacy and safety of a single intra-articular injection of non-animal stabilized hyaluronic acid (NASHA) in patients with osteoarthritis of the knee. Osteoarthritis Cartilage. 2004;12(8):642-649.
73. Arden NK, Akermark C, Andersson M, Todman MG, Altman RD. A randomized saline-controlled trial of NASHA hyaluronic acid for knee osteoarthritis. Current medical research and opinion. 2014;30(2):279-286.
74. Qaseem A, Wilt TJ, McLean RM, Forciea MA, Clinical Guidelines Committee of the American College of P. Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians. Annals of internal medicine. 2017;166(7):514-530.
75. Last AR, Hulbert K. Chronic low back pain: evaluation and management. Am Fam Physician. 2009;79(12):1067-1074.
76. Chou R, Qaseem A, Snow V, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. Annals of internal medicine. 2007;147(7):478-491.
77. Ballantyne JC. Opioid therapy in chronic pain. Phys Med Rehabil Clin N Am. 2015;26(2):201-218.
78. Khoueir P, Black MH, Crookes PF, Kaufman HS, Katkhouda N, Wang MY. Prospective assessment of axial back pain symptoms before and after bariatric weight reduction surgery. Spine J. 2009;9(6):454-463.
79. Roffey DM, Ashdown LC, Dornan HD, et al. Pilot evaluation of a multidisciplinary, medically supervised, nonsurgical weight loss program on the severity of low back pain in obese adults. Spine J. 2011;11(3):197-204.
80. Hall AM, Maher CG, Lam P, Ferreira M, Latimer J. Tai chi exercise for treatment of pain and disability in people with persistent low back pain: a randomized controlled trial. Arthritis Care Res (Hoboken). 2011;63(11):1576-1583.
81. Weifen W, et al. Effectivenes of tai chi practice for non-specific chronic low back pain on retired athletes: a randomized controlled study. J Musculoskeletal Pain. 2013;21(1):37-45.
82. Saper RB, Lemaster C, Delitto A, et al. Yoga, Physical Therapy, or Education for Chronic Low Back Pain: A Randomized Noninferiority Trial. Annals of internal medicine. 2017;167(2):85-94.
83. Bussing A, Ostermann T, Ludtke R, Michalsen A. Effects of yoga interventions on pain and pain-associated disability: a meta-analysis. J Pain. 2012;13(1):1-9.
84. Wieland LS, Skoetz N, Pilkington K, Vempati R, D'Adamo CR, Berman BM. Yoga treatment for chronic non-specific low back pain. The Cochrane database of systematic reviews. 2017;12(1).
85. Cherkin DC, Sherman KJ, Balderson BH, et al. Effect of Mindfulness-Based Stress Reduction vs Cognitive Behavioral Therapy or Usual Care on Back Pain and Functional Limitations in Adults With Chronic Low Back Pain: A Randomized Clinical Trial. Jama. 2016;315(12):1240-1249.
86. Zeidan F, Salomons T, Farris SR, et al. Neural mechanisms supporting the relationship between dispositional mindfulness and pain. Pain. 2018;159(12):2477-2485.
87. Furlan AD, Giraldo M, Baskwill A, Irvin E, Imamura M. Massage for low-back pain. The Cochrane database of systematic reviews. 2015;1(9).
88. Deyo RA, Walsh NE, Martin DC, Schoenfeld LS, Ramamurthy S. A controlled trial of transcutaneous electrical nerve stimulation (TENS) and exercise for chronic low back pain. N Engl J Med. 1990;322(23):1627-1634.
89. Hickey RF. Chronic low back pain: a comparison of diflunisal with paracetamol. N Z Med J. 1982;95(707):312-314.
90. Stein D, Peri T, Edelstein E, Elizur A, Floman Y. The efficacy of amitriptyline and acetaminophen in the management of acute low back pain. Psychosomatics. 1996;37(1):63-70.
91. Davies RA, Maher CG, Hancock MJ. A systematic review of paracetamol for non-specific low back pain. Eur Spine J. 2008;17(11):1423-1430.
92. Saragiotto BT, Machado GC, Ferreira ML, Pinheiro MB, Abdel Shaheed C, Maher CG. Paracetamol for low back pain. The Cochrane database of systematic reviews. 2016(6):CD012230.
93. Enthoven WT, Roelofs PD, Deyo RA, van Tulder MW, Koes BW. Non-steroidal anti-inflammatory drugs for chronic low back pain. The Cochrane database of systematic reviews. 2016;10(2).
94. Chou R, Deyo R, Friedly J, et al. Systemic Pharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline. Annals of internal medicine. 2017;166(7):480-492.
95. Skljarevski V, Zhang S, Desaiah D, et al. Duloxetine versus placebo in patients with chronic low back pain: a 12-week, fixed-dose, randomized, double-blind trial. J Pain. 2010;11(12):1282-1290.
96. Shanthanna H, Gilron I, Rajarathinam M, et al. Benefits and safety of gabapentinoids in chronic low back pain: A systematic review and meta-analysis of randomized controlled trials. PLoS Med. 2017;14(8).
97. Rivera CE. Lumbar Epidural Steroid Injections. Physical medicine and rehabilitation clinics of North America. 2018;29(1):73-92.
98. Manchikanti L, et al. Epidural interventions in the management of chronic spinal pain: American Society of Interventional pain physicians (ASIPP) Comprehensive Evidence-Based Guidelines. Pain Physician. 2021;24:S27-S208.
99. Fairbank J, Frost H, Wilson-MacDonald J, Yu LM, Barker K, Collins R. Randomised controlled trial to compare surgical stabilisation of the lumbar spine with an intensive rehabilitation programme for patients with chronic low back pain: the MRC spine stabilisation trial. Bmj. 2005;330(7502):23.
100. American Diabetes Association. Standards of medical care in diabetes. Diabetes Care. 2019;42(Suppl. 1):S124-138.
101. Callaghan BC, Cheng HT, Stables CL, Smith AL, Feldman EL. Diabetic neuropathy: clinical manifestations and current treatments. Lancet Neurol. 2012;11(6):521-534.
102. Ahn S, Song R. Effects of Tai Chi Exercise on glucose control, neuropathy scores, balance, and quality of life in patients with type 2 diabetes and neuropathy. J Altern Complement Med. 2012;18(12):1172-1178.
103. Abuaisha BB, Costanzi JB, Boulton AJ. Acupuncture for the treatment of chronic painful peripheral diabetic neuropathy: a long-term study. Diabetes Res Clin Pract. 1998;39(2):115-121.
104. Gok Metin Z, Arikan Donmez A, Izgu N, Ozdemir L, Arslan IE. Aromatherapy Massage for Neuropathic Pain and Quality of Life in Diabetic Patients. J Nurs Scholarsh. 2017;49(4):379-388.
105. Garrow AP, Xing M, Vere J, Verrall B, Wang L, Jude EB. Role of acupuncture in the management of diabetic painful neuropathy (DPN): a pilot RCT. Acupunct Med. 2014;32(3):242-249.
106. Jin DM, Xu Y, Geng DF, Yan TB. Effect of transcutaneous electrical nerve stimulation on symptomatic diabetic peripheral neuropathy: a meta-analysis of randomized controlled trials. Diabetes Res Clin Pract. 2010;89(1):10-15.
107. Gossrau G, Wahner M, Kuschke M, et al. Microcurrent transcutaneous electric nerve stimulation in painful diabetic neuropathy: a randomized placebo-controlled study. Pain medicine. 2011;12(6):953-960.
108. Otis JD, Sanderson K, Hardway C, Pincus M, Tun C, Soumekh S. A randomized controlled pilot study of a cognitive-behavioral therapy approach for painful diabetic peripheral neuropathy. J Pain. 2013;14(5):475-482.
109. Teixeira E. The effect of mindfulness meditation on painful diabetic peripheral neuropathy in adults older than 50 years. Holist Nurs Pract. 2010;24(5):277-283.

110. Griebeler ML, Morey-Vargas OL, Brito JP, et al. Pharmacologic interventions for painful diabetic neuropathy: An umbrella systematic review and comparative effectiveness network meta-analysis. Annals of internal medicine. 2014;161(9):639-649.
111. Goldstein DJ, Lu Y, Detke MJ, Lee TC, Iyengar S. Duloxetine vs. placebo in patients with painful diabetic neuropathy. Pain. 2005;116(1-2):109-118.
112. Wiffen PJ, Derry S, Moore RA, Kalso EA. Carbamazepine for chronic neuropathic pain and fibromyalgia in adults. The Cochrane database of systematic reviews. 2014;10(4).
113. Derry S, Bell RF, Straube S, Wiffen PJ, Aldington D, Moore RA. Pregabalin for neuropathic pain in adults. The Cochrane database of systematic reviews. 2019;1:CD007076.
114. Baron R, Mayoral V, Leijon G, Binder A, Steigerwald I, Serpell M. 5% lidocaine medicated plaster versus pregabalin in post-herpetic neuralgia and diabetic polyneuropathy: an open-label, non-inferiority two-stage RCT study. Current medical research and opinion. 2009;25(7):1663-1676.
115. Wilsey B, Marcotte T, Tsodikov A, et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. J Pain. 2008;9(6):506-521.
116. Toth C, Mawani S, Brady S, et al. An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. Pain. 2012;153(10):2073-2082.
117. Wallace MS, Marcotte TD, Umlauf A, Gouaux B, Atkinson JH. Efficacy of Inhaled Cannabis on Painful Diabetic Neuropathy. J Pain. 2015;16(7):616-627.
118. Selvarajah D, Gandhi R, Emery CJ, Tesfaye S. Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding factor. Diabetes Care. 2010;33(1):128-130.
119. GW Pharmaceuticals. A study of Sativex® for pain relief due to diabetic neuropathy. NCT00710424. 2008; Vol. 2017 (Clinicaltrials.gov).
120. Mendell JR, Sahenk Z. Clinical practice. Painful sensory neuropathy. N Engl J Med. 2003;348(13):1243-1255.
121. Treatment of painful diabetic neuropathy with topical capsaicin: A multicenter, double-blind, vehicle-controlled study. Archives of internal medicine. 1991;151(11):2225-2229.
122. Tandan R, Lewis GA, Krusinski PB, Badger GB, Fries TJ. Topical capsaicin in painful diabetic neuropathy. Controlled study with long-term follow-up. Diabetes Care. 1992;15(1):8-14.
123. Waldfogel JM, Nesbit SA, Dy SM, et al. Pharmacotherapy for diabetic peripheral neuropathy pain and quality of life: A systematic review. Neurology. 2017;88(20):1958-1967.
124. Macfarlane GJ, Kronisch C, Dean LE, et al. EULAR revised recommendations for the management of fibromyalgia. Ann Rheum Dis. 2017;76(2):318-328.
125. American College of Rheumatology. Fibromyalgia treatment. https://www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Fibromyalgia. Published 2019. Accessed May 24 2019.
126. Jones KD, Adams D, Winters-Stone K, Burckhardt CS. A comprehensive review of 46 exercise treatment studies in fibromyalgia (1988-2005). Health Qual Life Outcomes. 2006;4:67.
127. Andrade A, de Azevedo Klumb Steffens R, Sieczkowska SM, Peyre Tartaruga LA, Torres Vilarino G. A systematic review of the effects of strength training in patients with fibromyalgia: clinical outcomes and design considerations. Adv Rheumatol. 2018;58(1):36.
128. Bidonde J, Busch AJ, Schachter CL, et al. Aerobic exercise training for adults with fibromyalgia. The Cochrane database of systematic reviews. 2017;21(6).
129. Busch AJ, Webber SC, Richards RS, et al. Resistance exercise training for fibromyalgia. Cochrane Database Syst Rev. 2013;20(12).
130. Wang C, Schmid CH, Rones R, et al. A randomized trial of tai chi for fibromyalgia. N Engl J Med. 2010;363(8):743-754.
131. Deare JC, Zheng Z, Xue CC, et al. Acupuncture for treating fibromyalgia. The Cochrane database of systematic reviews. 2013;31(5).
132. Yuan SL, Matsutani LA, Marques AP. Effectiveness of different styles of massage therapy in fibromyalgia: a systematic review and meta-analysis. Manual therapy. 2015;20(2):257-264.
133. Salazar AP, Stein C, Marchese RR, Plentz RD, Pagnussat AS. Electric Stimulation for Pain Relief in Patients with Fibromyalgia: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Pain physician. 2017;20(2):15-25.
134. Bernardy K, Klose P, Busch AJ, Choy EH, Hauser W. Cognitive behavioural therapies for fibromyalgia. Cochrane Database Syst Rev. 2013;10(9).
135. Derry S, Wiffen PJ, Hauser W, et al. Oral nonsteroidal anti-inflammatory drugs for fibromyalgia in adults. The Cochrane database of systematic reviews. 2017;27(3).
136. Lunn MP, Hughes RA, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. The Cochrane database of systematic reviews. 2014;1:CD007115.
137. Cording M, Derry S, Phillips T, Moore RA, Wiffen PJ. Milnacipran for pain in fibromyalgia in adults. The Cochrane database of systematic reviews. 2015(10):CD008244.
138. Welsch P, Uceyler N, Klose P, Walitt B, Hauser W. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia. The Cochrane database of systematic reviews. 2018;2:CD010292.
139. Hauser W, Petzke F, Uceyler N, Sommer C. Comparative efficacy and acceptability of amitriptyline, duloxetine and milnacipran in fibromyalgia syndrome: a systematic review with meta-analysis. Rheumatology. 2011;50(3):532-543.
140. Walitt B, Urrutia G, Nishishinya MB, Cantrell SE, Hauser W. Selective serotonin reuptake inhibitors for fibromyalgia syndrome. The Cochrane database of systematic reviews. 2015;5(6).
141. Uceyler N, Sommer C, Walitt B, Hauser W. Anticonvulsants for fibromyalgia. The Cochrane database of systematic reviews. 2013;16(10).
142. Gilron I, Chaparro LE, Tu D, et al. Combination of pregabalin with duloxetine for fibromyalgia: a randomized controlled trial. Pain. 2016;157(7):1532-1540.
143. Arnold LM, Goldenberg DL, Stanford SB, et al. Gabapentin in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled, multicenter trial. Arthritis Rheum. 2007;56(4):1336-1344.
144. Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the treatment of pain in fibromyalgia. J Pain. 2008;9(2):164-173.
145. Ware MA, Fitzcharles MA, Joseph L, Shir Y. The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. Anesthesia and analgesia. 2010;110(2):604-610.

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. Which of the following statements is true about a functional approach to treating painful conditions?
- A. An example of a function-based treatment goal is a 20% reduction in reported pain on a 1-10 pain assessment scale.
- B. Progress toward function-based goals can be monitored using a variety of pain-assessment scales.
- C. Relatively modest reductions in pain can lead to significant functional improvements.
- D. The goal of a function-based treatment plan is for the patient to report no pain on pain assessment scales.

12. One guiding principle of creating function-based goals is:
- A. Set goals based on consensus recommendations from professional organizations.
- B. Choose goals that all patients could realistically be expected to achieve eventually, such as walking for 30 minutes a day.
- C. Goals should be framed in terms of percentage gains or reductions on pain assessment scales.
- D. It is better to set goals slightly too low than slightly too high.

13. Which of the following is *not* an example of multimodal therapy for acute pain?
- A. Systemic NSAID plus systemic opioid.
- B. Epidural opioid plus local anesthetic.
- C. Immediate-release opioid plus extended-release opioid.
- D. Acetaminophen plus opioid.

14. Which statement is true about a general approach to initiating any kind of treatment for a painful condition?
- A. Begin treatment with the analgesic whose strength is best matched to the patient's reported pain intensity.
- B. It is acceptable to begin pain treatment before the source is determined.
- C. Create function-based treatment plans for all patients with a painful condition.
- D. Use signed patient/clinician agreements with all patients treated for a chronic pain condition.

15. Non-pharmacologic methods for treating acute pain are appropriate for which phase of healing?
- A. Immediately after tissue trauma.
- B. > 48 hours after tissue trauma.
- C. Late healing phase for recovery of function.
- D. Immediately after tissue trauma as well as in late healing phase.

16. Which class of non-opioid medications can be effective for treating diabetes-related neuropathic pain?
- A. Anticonvulsants.
- B. NSAIDs.
- C. Cannabinoids.
- D. Calcium channel blockers.

17. Which non-opioid drug, or drug class, has shown efficacy in the treatment of acute pain associated with sickle cell crises, renal colic, and trauma?
- A. Cannabis.
- B. NSAIDs.
- C. Ketamine.
- D. Anticonvulsants.

18. Which of the following types of antidepressants may be effective for treating chronic non-cancer pain?
- A. SSRIs.
- B. Serotonin/norepinephrine inhibitors.
- C. Tricyclics.
- D. SSRIs, SNRIs, and tricyclics.

19. Which phrase best characterizes the evidence base for acupuncture as a pain treatment for hip osteoarthritis?
- A. Mostly supportive evidence.
- B. Mixed evidence.
- C. Mostly disconfirming evidence.
- D. Evidence only from observational studies.

20. Current guidelines for treating chronic low back pain recommend:
- A. Match the strength of an analgesic to the level of pain reported by the patient.
- B. Try exercise and weight loss first, followed by physical therapy or a non-opioid pharmacological analgesic.
- C. Try nonpharmacological options first, followed by treatment with an NSAID.
- D. Try a combination of an NSAID and acetaminophen first, followed by muscle relaxants.

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.

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 12 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

FACULTY

Stephen Braun
Medical Writer
Braun Medical Communications

ACTIVITY PLANNER

Michael Brooks
CME Director
InforMed

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

12

AMA PRA CATEGORY 1 CREDITS™

This course awards twelve (12) *AMA PRA Category 1 Credits™*.

Physicians maintaining a current Kentucky medical license are required to complete sixty (60) hours of CME every three (3) year cycle, with thirty (30) hours being Category 1.

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:

- Stephen Braun
- Michael Brooks

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.

ACKNOWLEDGMENTS

This learning activity was adapted from "*Making Healthcare Safer III: A Critical Analysis of Existing and Emerging Patient Safety Practices*". AHRQ Publication No. 20-0029-EF. Rockville, MD: Agency for Healthcare Research and Quality; March 2020.

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.

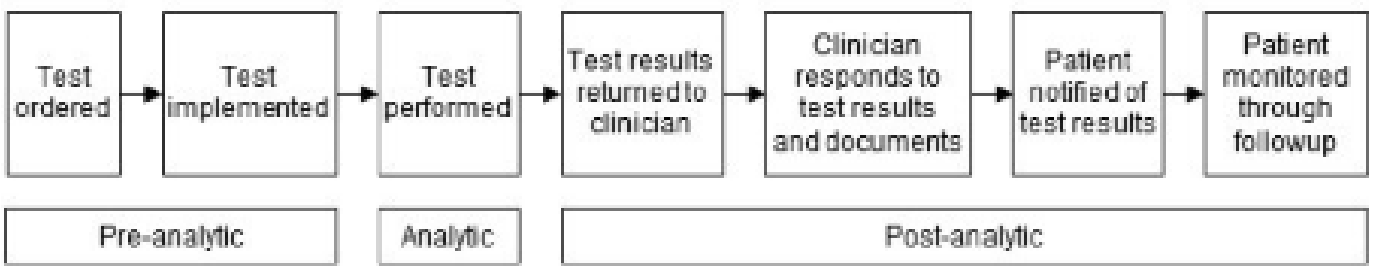
Cook et al. (2010) conducted a meta-analysis and systematic review of the effects on training outcomes of using virtual patients, including the effects on clinical reasoning.[14] The learners interact with a computer program that simulates real-life clinical scenarios to obtain a history, conduct a physical 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.

References

1. Singh H, Meyer AN, Thomas EJ. The frequency of diagnostic errors in outpatient care: estimations from three large observational studies involving US adult populations. BMJ Qual Saf. 2014;23(9):727-731.
2. Zwaan L, de Bruijne M, Wagner C, et al. Patient record review of the incidence, consequences, and causes of diagnostic adverse events. Arch Intern Med. 2010;170(12):1015-1021.
3. Saber Tehrani AS, Lee H, Mathews SC, et al. 25-Year summary of US malpractice claims for diagnostic errors 1986-2010: an analysis from the National Practitioner Data Bank. BMJ Qual Saf. 2013;22(8):672-680.
4. National Academies of Sciences Engineering and Medicine. Improving Diagnosis in Health Care. Washington, DC2015.
5. Herweh C, Ringleb PA, Rauch G, et al. Performance of e-ASPECTS software in comparison to that of stroke physicians on assessing CT scans of acute ischemic stroke patients. Int J Stroke. 2016;11(4):438-445.
6. Bien N, Rajpurkar P, Ball RL, et al. Deep-learning-assisted diagnosis for knee magnetic resonance imaging: Development and retrospective validation of MRNet. PLoS Med. 2018;15(11):e1002699.
7. Li C, Jing B, Ke L, et al. Development and validation of an endoscopic images-based deep learning model for detection with nasopharyngeal malignancies. Cancer Commun (Lond). 2018;38(1):59.
8. Vandenberghe ME, Scott ML, Scorer PW, Soderberg M, Balcerzak D, Barker C. Relevance of deep learning to facilitate the diagnosis of HER2 status in breast cancer. Sci Rep. 2017;7:45938.
9. Xiong Y, Ba X, Hou A, Zhang K, Chen L, Li T. Automatic detection of mycobacterium tuberculosis using artificial intelligence. J Thorac Dis. 2018;10(3):1936-1940.
10. Campbell R. The five "rights" of clinical decision support. J AHIMA. 2013;84(10):42-47; quiz 48.
11. The Joint Commission. Hospital: 2021 National Patient Safety Goals. https://www.jointcommission.org/standards/national-patient-safety-goals/hospital-national-patient-safety-goals/. Published 2021. Accessed October 12, 2021.
12. Etchells E, Adhikari NK, Cheung C, et al. Real-time clinical alerting: effect of an automated paging system on response time to critical laboratory values--a randomised controlled trial. Qual Saf Health Care. 2010;19(2):99-102.
13. Dalal AK, Roy CL, Poon EG, et al. Impact of an automated email notification system for results of tests pending at discharge: a cluster-randomized controlled trial. J Am Med Inform Assoc. 2014;21(3):473-480.
14. Cook DA, Erwin PJ, Triola MM. Computerized virtual patients in health professions education: a systematic review and meta-analysis. Acad Med. 2010;85(10):1589-1602.
15. Wolpaw T, Papp KK, Bordage G. Using SNAPPS to facilitate the expression of clinical reasoning and uncertainties: a randomized comparison group trial. Acad Med. 2009;84(4):517-524.
16. Smith BW, Slack MB. The effect of cognitive debiasing training among family medicine residents. Diagnosis (Berl). 2015;2(2):117-121.
17. Mohan D, Fischhoff B, Angus DC, et al. Serious games may improve physician heuristics in trauma triage. Proc Natl Acad Sci U S A. 2018;115(37):9204-9209.
18. Goodman TR, Kelleher M. Improving Novice Radiology Trainees' Perception Using Fine Art. J Am Coll Radiol. 2017;14(10):1337-1340.
19. Pusic MV, Andrews JS, Kessler DO, et al. Prevalence of abnormal cases in an image bank affects the learning of radiograph interpretation. Med Educ. 2012;46(3):289-298.
20. Geijer H, Geijer M. Added value of double reading in diagnostic radiology,a systematic review. Insights Imaging. 2018;9(3):287-301.
21. Natarajan V, Bosch P, Dede O, et al. Is There Value in Having Radiology Provide a Second Reading in Pediatric Orthopaedic Clinic? J Pediatr Orthop. 2017;37(4):e292-e295.
22. Murphy R, Slater A, Uberoi R, Bungay H, Ferrett C. Reduction of perception error by double reporting of minimal preparation CT colon. Br J Radiol. 2010;83(988):331-335.
23. Harvey HB, Alkasab TK, Prabhakar AM, et al. Radiologist Peer Review by Group Consensus. J Am Coll Radiol. 2016;13(6):656-662.
24. Itri JN, Donithan A, Patel SH. Random Versus Nonrandom Peer Review: A Case for More Meaningful Peer Review. J Am Coll Radiol. 2018;15(7):1045-1052.
25. Silber JH, Williams SV, Krakauer H, Schwartz JS. Hospital and patient characteristics associated with death after surgery. A study of adverse occurrence and failure to rescue. Med Care. 1992;30(7):615-629.
26. Berwick DM, Calkins DR, McCannon CJ, Hackbarth AD. The 100,000 lives campaign: setting a goal and a deadline for improving health care quality. JAMA. 2006;295(3):324-327.
27. Cardona-Morrell M, Prgomet M, Turner RM, Nicholson M, Hillman K. Effectiveness of continuous or intermittent vital signs monitoring in preventing adverse events on general wards: a systematic review and meta-analysis. Int J Clin Pract. 2016;70(10):806-824.
28. Maharaj R, Raffaele I, Wendon J. Rapid response systems: a systematic review and meta-analysis. Crit Care. 2015;19:254.
29. Solomon RS, Corwin GS, Barclay DC, Quddusi SF, Dannenberg MD. Effectiveness of rapid response teams on rates of in-hospital cardiopulmonary arrest and mortality: A systematic review and meta-analysis. J Hosp Med. 2016;11(6):438-445.
30. Chan PS, Jain R, Nallmothu BK, Berg RA, Sasson C. Rapid Response Teams: A Systematic Review and Meta-analysis. Arch Intern Med. 2010;170(1):18-26.
31. Chen J, Ou L, Flabouris A, Hillman K, Bellomo R, Parr M. Impact of a standardized rapid response system on outcomes in a large healthcare jurisdiction. Resuscitation. 2016;107:47-56.
32. Moriarty JP, Schiebel NE, Johnson MG, et al. Evaluating implementation of a rapid response team: considering alternative outcome measures. Int J Qual Health Care. 2014;26(1):49-57.
33. Bach TA, Berglund LM, Turk E. Managing alarm systems for quality and safety in the hospital setting. BMJ Open Qual. 2018;7(3):e000202.
34. Sendelbach S, Funk M. Alarm fatigue: a patient safety concern. AACN Adv Crit Care. 2013;24(4):378-386; quiz 387-378.
35. Allen J, Hileman K, Ward A. Simple solutions for improving patient safety in cardiac monitoring—eight critical elements to monitor alarm competency. https://www.aami.org/docs/default-source/foundation/alarms/2013_si_alarm_competency_upmc.pdf?sfvrsn=5d4681e6_2. Accessed October 21, 2021.
36. Rhee C, Dantes R, Epstein L, et al. Incidence and Trends of Sepsis in US Hospitals Using Clinical vs Claims Data, 2009-2014. JAMA. 2017;318(13):1241-1249.
37. Torio CM, Moore BJ. National Inpatient Hospital Costs: The most expensive conditions by payer, 2013. Agency for Healthcare Research and Quality Statistical Brief #204. 2013.
38. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med. 2017;43(3):304-377.
39. Smyth MA, Brace-McDonnell SJ, Perkins GD. Identification of adults with sepsis in the prehospital environment: a systematic review. BMJ Open. 2016;6(8):e011218.
40. Hunter CL, Silvestri S, Ralls G, et al. Comparing Quick Sequential Organ Failure Assessment Scores to End-tidal Carbon Dioxide as Mortality Predictors in Prehospital Patients with Suspected Sepsis. West J Emerg Med. 2018;19(3):446-451.
41. Tedesco ER, Whiteman K, Heuston M, Swanson-Biearman B, Stephens K. Interprofessional Collaboration to Improve Sepsis Care and Survival Within a Tertiary Care Emergency Department. J Emerg Nurs. 2017;43(6):532-538.

42. Larosa JA, Ahmad N, Feinberg M, Shah M, Dibrienza R, Studer S. The use of an early alert system to improve compliance with sepsis bundles and to assess impact on mortality. Crit Care Res Pract. 2012;2012:980369.
43. Gatewood MO, Wemple M, Greco S, Kritek PA, Durvasula R. A quality improvement project to improve early sepsis care in the emergency department. BMJ Qual Saf. 2015;24(12):787-795.
44. Centers for Disease Control and Prevention. What is C. diff? https://www.cdc.gov/cdiff/what-is.html. Accessed October 15, 2021.
45. Magill SS, Edwards JR, Bamberg W, et al. Multistate point-prevalence survey of health care-associated infections. N Engl J Med. 2014;370(13):1198-1208.
46. Zhang D, Prabhu VS, Marcella SW. Attributable Healthcare Resource Utilization and Costs for Patients With Primary and Recurrent Clostridium difficile Infection in the United States. Clin Infect Dis. 2018;66(9):1326-1332.
47. Luo R, Barlam TF. Ten-year review of Clostridium difficile infection in acute care hospitals in the USA, 2005-2014. J Hosp Infect. 2018;98(1):40-43.
48. Centers for Disease Control and Prevention. Core elements of hospital antibiotic stewardship programs. https://www.cdc.gov/antibiotic-use/core-elements/hospital.html. Accessed October 17, 2021.
49. Ticinesi A, Nouvenne A, Folesani G, et al. Multimorbidity in elderly hospitalised patients and risk of Clostridium difficile infection: a retrospective study with the Cumulative Illness Rating Scale (CIRS). BMJ Open. 2015;5(10):e009316.
50. Centers for Disease Control and Prevention. Projected incidence of infections and deaths due to antibiotic resistant healthcare-associated infections. https://www.cdc.gov/hai/data/archive/stop-spread-technical-appendix.html. Accessed October 16, 2021.
51. Centers for Disease Control and Prevention. Data summary of HAIs in the U.S.: Assessing progress 2006-2016. https://www.cdc.gov/hai/data/archive/data-summary-assessing-progress.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fhai%2Fsurveillance%2Fdata-reports%2Fdata-summary-assessing-progress.html. Accessed October 16, 2021.
52. Feazel LM, Malhotra A, Perencevich EN, Kaboli P, Diekema DJ, Schweizer ML. Effect of antibiotic stewardship programmes on Clostridium difficile incidence: a systematic review and meta-analysis. J Antimicrob Chemother. 2014;69(7):1748-1754.
53. Shea KM, Hobbs ALV, Jaso TC, et al. Effect of a Health Care System Respiratory Fluoroquinolone Restriction Program To Alter Utilization and Impact Rates of Clostridium difficile Infection. Antimicrob Agents Chemother. 2017;61(6).
54. Dancer SJ, Kirkpatrick P, Corcoran DS, Christison F, Farmer D, Robertson C. Approaching zero: temporal effects of a restrictive antibiotic policy on hospital-acquired Clostridium difficile, extended-spectrum beta-lactamase-producing coliforms and meticillin-resistant Staphylococcus aureus. Int J Antimicrob Agents. 2013;41(2):137-142.
55. Talpaert MJ, Gopal Rao G, Cooper BS, Wade P. Impact of guidelines and enhanced antibiotic stewardship on reducing broad-spectrum antibiotic usage and its effect on incidence of Clostridium difficile infection. J Antimicrob Chemother. 2011;66(9):2168-2174.
56. Yam P, Fales D, Jemison J, Gillum M, Bernstein M. Implementation of an antimicrobial stewardship program in a rural hospital. Am J Health Syst Pharm. 2012;69(13):1142-1148.
57. McDonald LC, Gerding DN, Johnson S, et al. Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. 2018;66(7):e1-e48.
58. Oughton MT, Loo VG, Dendukuri N, Fenn S, Libman MD. Hand hygiene with soap and water is superior to alcohol rub and antiseptic wipes for removal of Clostridium difficile. Infect Control Hosp Epidemiol. 2009;30(10):939-944.
59. Bearman G, Rosato AE, Duane TM, et al. Trial of universal gloving with emollient-impregnated gloves to promote skin health and prevent the transmission of multidrug-resistant organisms in a surgical intensive care unit. Infect Control Hosp Epidemiol. 2010;31(5):491-497.
60. Landelle C, Verachten M, Legrand P, Girou E, Barbut F, Brun-Buisson C. Contamination of healthcare workers' hands with Clostridium difficile spores after caring for patients with C. difficile infection. Infect Control Hosp Epidemiol. 2014;35(1):10-15.
61. Erasmus V, Daha TJ, Brug H, et al. Systematic review of studies on compliance with hand hygiene guidelines in hospital care. Infect Control Hosp Epidemiol. 2010;31(3):283-294.
62. Sunkesula VC, Knighton S, Zabarsky TF, Kundrapu S, Higgins PA, Donskey CJ. Four Moments for Patient Hand Hygiene: A Patient-Centered, Provider-Facilitated Model to Improve Patient Hand Hygiene. Infect Control Hosp Epidemiol. 2015;36(8):986-989.
63. Tomas ME, Sunkesula VC, Kundrapu S, Wilson BM, Donskey CJ. An intervention to reduce health care personnel hand contamination during care of patients with Clostridium difficile infection. Am J Infect Control. 2015;43(12):1366-1367.
64. Trick WE, Lin MY, Cheng-Leidig R, et al. Electronic Public Health Registry of Extensively Drug-Resistant Organisms, Illinois, USA. Emerg Infect Dis. 2015;21(10):1725-1732.
65. Centers for Disease Control and Prevention. Containing unusual resistance https://www.cdc.gov/vitalsigns/pdf/2018-04-vitalsigns.pdf. Accessed October 30, 2021.
66. Duszynska W, Adamik B, Lentka-Bera K, et al. Effect of universal chlorhexidine decolonisation on the infection rate in intensive care patients. Anaesthesiol Intensive Ther. 2017;49(1):28-33.
67. Wittekamp BH, Plantinga NL, Cooper BS, et al. Decontamination Strategies and Bloodstream Infections With Antibiotic-Resistant Microorganisms in Ventilated Patients: A Randomized Clinical Trial. JAMA. 2018;320(20):2087-2098.
68. Centers for Disease Control and Prevention. Interim guidance for a public health response to contain novel or targeted multidrug-resistant organisms. https://www.cdc.gov/hai/pdfs/containment/Health-Response-Contain-MDRO-H.pdf. Accessed October 30, 2021.
69. Riggs MM, Sethi AK, Zabarsky TF, Eckstein EC, Jump RL, Donskey CJ. Asymptomatic carriers are a potential source for transmission of epidemic and nonepidemic Clostridium difficile strains among long-term care facility residents. Clin Infect Dis. 2007;45(8):992-998.
70. Wilcox MH, Fawley WN. Hospital disinfectants and spore formation by Clostridium difficile. Lancet. 2000;356(9238):1324.
71. Fawley WN, Underwood S, Freeman J, et al. Efficacy of hospital cleaning agents and germicides against epidemic Clostridium difficile strains. Infect Control Hosp Epidemiol. 2007;28(8):920-925.
72. Levin J, Riley LS, Parrish C, English D, Ahn S. The effect of portable pulsed xenon ultraviolet light after terminal cleaning on hospital-associated Clostridium difficile infection in a community hospital. Am J Infect Control. 2013;41(8):746-748.
73. Oldfield EI, Oldfield EC, III, Johnson DA. Clinical update for the diagnosis and treatment of Clostridium difficile infection. World J Gastrointest Pharmacol Ther. 2014;5(1):1-26.
74. Power M, Wigglesworth N, Donaldson E, Chadwick P, Gillibrand S, Goldmann D. Reducing Clostridium difficile infection in acute care by using an improvement collaborative. BMJ. 2010;341:c3359.
75. Weiner LM, Webb AK, Limbago B, et al. Antimicrobial-Resistant Pathogens Associated With Healthcare-Associated Infections: Summary of Data Reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011-2014. Infect Control Hosp Epidemiol. 2016;37(11):1288-1301.
76. Patel PK, Gupta A, Vaughn VM, Mann JD, Ameling JM, Meddings J. Review of Strategies to Reduce Central Line-Associated Bloodstream Infection (CLABSI) and Catheter-Associated Urinary Tract Infection (CAUTI) in Adult ICUs. J Hosp Med. 2018;13(2):105-116.

77. Gould CV, Umscheid CA, Agarwal RK, Kuntz G, Pegues DA, Healthcare Infection Control Practices Advisory C. Guideline for prevention of catheter-associated urinary tract infections 2009. Infect Control Hosp Epidemiol. 2010;31(4):319-326.
78. Mody L, Greene MT, Meddings J, et al. A National Implementation Project to Prevent Catheter-Associated Urinary Tract Infection in Nursing Home Residents. JAMA Intern Med. 2017;177(8):1154-1162.
79. Doyle JS, Buising KL, Thursky KA, Worth LJ, Richards MJ. Epidemiology of infections acquired in intensive care units. Semin Respir Crit Care Med. 2011;32(2):115-138.
80. Dixon JJ, Steele M, Makanjuola AD. Antimicrobial locks increase the prevalence of Staphylococcus aureus and antibiotic-resistant Enterobacter: observational retrospective cohort study. Nephrol Dial Transplant. 2012;27(9):3575-3581.
81. Klompas M, Branson R, Eichenwald EC, et al. Strategies to prevent ventilator-associated pneumonia in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol. 2014;35(8):915-936.
82. Camus C, Salomon S, Bouchigny C, et al. Short-term decline in all-cause acquired infections with the routine use of a decontamination regimen combining topical polymyxin, tobramycin, and amphotericin B with mupirocin and chlorhexidine in the ICU: a single-center experience. Crit Care Med. 2014;42(5):1121-1130.
83. Institute of Medicine. Preventing medication errors: Quality Chasm Series. Washington DC: National Academies Press; 2006.
84. Wolf ZR. Strategies to Reduce Patient Harm From Infusion-Associated Medication Errors: A Scoping Review. J Infus Nurs. 2018;36(1):58-65.
85. Giuliano KK. IV Smart Pumps: The Impact of a Simplified User Interface on Clinical Use. Biomed Instrum Technol. 2015;Suppl:13-21.
86. Tomczyk S, Zanichelli V, Grayson ML, et al. Control of Carbapenem-resistant Enterobacteriaceae, Acinetobacter baumannii, and Pseudomonas aeruginosa in Healthcare Facilities: A Systematic Review and Reanalysis of Quasi-experimental Studies. Clin Infect Dis. 2019;68(5):873-884.
87. European Center for Disease Prevention and Control. Systematic Review of the Effectiveness of Infection Control Measures To Prevent the Transmission of Carbapenemase-Producing Enterobacteriaceae Through Cross-Border Transfer of Patients. https://www.ecdc.europa.eu/en/publications-data/systematic-review-effectiveness-infection-control-measures-prevent-transmission. Accessed October 20, 2021.
88. Goodman KE, Simner PJ, Klein EY, et al. How frequently are hospitalized patients colonized with carbapenem-resistant Enterobacteriaceae (CRE) already on contact precautions for other indications? Infect Control Hosp Epidemiol. 2018;39(12):1491-1493.
89. Borer A, Eskira S, Nativ R, et al. A multifaceted intervention strategy for eradication of a hospital-wide outbreak caused by carbapenem-resistant Klebsiella pneumoniae in Southern Israel. Infect Control Hosp Epidemiol. 2011;32(12):1158-1165.
90. The Joint Commission. Hot Topics: Transitions of Care: the need for a more effective approach to continuing patient care. https://pdf4pro.com/view/hot-topics-transitions-of-care-joint-commission-c1f98.html. Accessed October 20, 2021.
91. Watts E, Rayman G, Diabetes UK. Making Hospitals Safe for Diabetes Patients. https://www.diabetes.org.uk/resources-s3/2018-10/Making%20Hospitals%20safe%20for%20people%20with%20diabetes_FINAL.pdf. Accessed October 20, 2021.
92. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345(19):1359-1367.
93. National Center for Health Statistics. Health, United States, 2016: With Chartbook on long-term trends in health. 2017.
94. Classen DC, Jaser L, Budnitz DS. Adverse drug events among hospitalized Medicare patients: epidemiology and national estimates from a new approach to surveillance. Jt Comm J Qual Patient Saf. 2010;36(1):12-21.
95. Ocampo CC, Garcia-Cardenas V, Martinez-Martinez F, Benrimoj SI, Amariles P, Gastelurrutia MA. Implementation of medication review with follow-up in a Spanish community pharmacy and its achieved outcomes. Int J Clin Pharm. 2015;37(5):931-940.
96. Ailabouni N, Mangin D, Nishtala PS. DEFEAT-polypharmacy: deprescribing anticholinergic and sedative medicines feasibility trial in residential aged care facilities. Int J Clin Pharm. 2019;41(1):167-178.
97. Petersen AW, Shah AS, Simmons SF, et al. Shed-MEDS: pilot of a patient-centered deprescribing framework reduces medications in hospitalized older adults being transferred to inpatient postacute care. Ther Adv Drug Saf. 2018;9(9):523-533.
98. McKean M, Pillans P, Scott IA. A medication review and deprescribing method for hospitalised older patients receiving multiple medications. Intern Med J. 2016;46(1):35-42.
99. Tannenbaum C, Martin P, Tamblyn R, Benedetti A, Ahmed S. Reduction of inappropriate benzodiazepine prescriptions among older adults through direct patient education: the EMPOWER cluster randomized trial. JAMA Intern Med. 2014;174(6):890-898.
100. Martin P, Tamblyn R, Benedetti A, Ahmed S, Tannenbaum C. Effect of a Pharmacist-Led Educational Intervention on Inappropriate Medication Prescriptions in Older Adults: The D-PRESCRIBE Randomized Clinical Trial. JAMA. 2018;320(18):1889-1898.
101. Lenander C, Elfsson B, Danielsson B, Midlov P, Hasselstrom J. Effects of a pharmacist-led structured medication review in primary care on drug-related problems and hospital admission rates: a randomized controlled trial. Scand J Prim Health Care. 2014;32(4):180-186.
102. Chan DC, Chen JH, Wen CJ, Chiu LS, Wu SC. Effectiveness of the medication safety review clinics for older adults prescribed multiple medications. J Formos Med Assoc. 2014;113(2):106-113.
103. Campins L, Serra-Prat M, Gozalo I, et al. Randomized controlled trial of an intervention to improve drug appropriateness in community-dwelling polymedicated elderly people. Fam Pract. 2017;34(1):36-42.
104. Gibert P, Cabaret M, Moulis M, et al. Optimizing medication use in elderly people in primary care: Impact of STOPP criteria on inappropriate prescriptions. Arch Gerontol Geriatr. 2018;75:16-19.
105. Hannou S, Voirol P, Pannatier A, et al. Pharmacist intervention acceptance for the reduction of potentially inappropriate drug prescribing in acute psychiatry. Int J Clin Pharm. 2017;39(6):1228-1236.
106. Centers for Disease Control & Prevention. Understanding the epidemic. https://www.cdc.gov/drugoverdose/epidemic/index.html. Published 2019. Accessed April 1 2019.
107. Centers for Disease Control & Prevention. Vital signs: overdoses of prescription opioid pain relievers---United States, 1999--2008. MMWR Morbidity and mortality weekly report. 2011;60(43):1487-1492.
108. Centers for Disease Control & Prevention. Increse in fatal drug overdoses across the United States driven by synthetic opioids before and during the COVID-19 pandemic. https://emergency.cdc.gov/han/2020/han00438.asp?ACSTrackingID=USCDC_511-DM44961&ACSTrackingLabel=HAN%20438%20-%20General%20Public&deliveryName=USCDC_511-DM44961. Accessed December 28, 2020.
109. Centers for Disease Control & Prevention. 12 Month-ending provisional number of drug overdose deaths. https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm. Accessed December 28, 2020.
110. Centers for Disease Control & Prevention. Opioid overdose: Understanding the Epidemic. https://www.cdc.gov/drugoverdose/images/3-waves-2019.PNG. Published 2021. Accessed June 10, 2021.

111. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain--United States, 2016. JAMA. 2016;315(15):1624-1645.
112. Weiner SG, Price CN, Atalay AJ, et al. A Health System-Wide Initiative to Decrease Opioid-Related Morbidity and Mortality. Jt Comm J Qual Patient Saf. 2019;45(1):3-13.
113. Substance Abuse and Mental Health Services Administration. Treatment improvement protocol 63: medication for opioid use disorder for healthcare and addiction professionals, policymakers, patients, and familier. https://store.samhsa.gov/product/TIP-63-Medications-for-Opioid-Use-Disorder-Full-Document/PEP21-02-01-002. Accessed October 21, 2021.
114. Liebschutz JM, Crooks D, Herman D, et al. Buprenorphine treatment for hospitalized, opioid-dependent patients: a randomized clinical trial. JAMA Intern Med. 2014;174(8):1369-1376.
115. Bannon L, McGaughey J, Verghis R, Clarke M, McAuley DF, Blackwood B. The effectiveness of non-pharmacological interventions in reducing the incidence and duration of delirium in critically ill patients: a systematic review and meta-analysis. Intensive Care Med. 2019;45(1):1-12.
116. Woodhouse R, Burton JK, Rana N, Pang YL, Lister JE, Siddiqi N. Interventions for preventing delirium in older people in institutional long-term care. Cochrane Database Syst Rev. 2019;4:CD009537.
117. Oh ES, Needham DM, Nikooie R, et al. Antipsychotics for Preventing Delirium in Hospitalized Adults: A Systematic Review. Ann Intern Med. 2019;171(7):474-484.
118. Pandharipande P, Jackson J, Ely EW. Delirium: acute cognitive dysfunction in the critically ill. Curr Opin Crit Care. 2005;11(4):360-368.
119. Oh ES, Fong TG, Hshieh TT, Inouye SK. Delirium in Older Persons: Advances in Diagnosis and Treatment. JAMA. 2017;318(12):1161-1174.
120. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet. 2014;383(9920):911-922.
121. Hansen LO, Greenwald JL, Budnitz T, et al. Project BOOST: effectiveness of a multihospital effort to reduce rehospitalization. J Hosp Med. 2013;8(8):421-427.
122. Parry C, Coleman EA, Smith JD, Frank J, Kramer AM. The care transitions intervention: a patient-centered approach to ensuring effective transfers between sites of geriatric care. Home Health Care Serv Q. 2003;22(3):1-17.
123. Hirschman KB, Shaid E, McCauley K, Pauly MV, Naylor MD. Continuity of Care: The Transitional Care Model. Online J Issues Nurs. 2015;20(3):1.
124. Stewart DW, Freshour JE. Aspirin for the prophylaxis of venous thromboembolic events in orthopedic surgery patients: a comparison of the AAOS and ACCP guidelines with review of the evidence. Ann Pharmacother. 2013;47(1):63-74.
125. Agaba P, Kildow BJ, Dhotar H, Seyler TM, Bolognesi M. Comparison of postoperative complications after total hip arthroplasty among patients receiving aspirin, enoxaparin, warfarin, and factor Xa inhibitors. J Orthop. 2017;14(4):537-543.
126. Anderson DR, Dunbar M, Murnaghan J, et al. Aspirin or Rivaroxaban for VTE Prophylaxis after Hip or Knee Arthroplasty. N Engl J Med. 2018;378(8):699-707.
127. Hamilton SC, Whang WW, Anderson BJ, Bradbury TL, Erens GA, Roberson JR. Inpatient enoxaparin and outpatient aspirin chemoprophylaxis regimen after primary hip and knee arthroplasty: a preliminary study. J Arthroplasty. 2012;27(9):1594-1598.
128. Deirmengian GK, Heller S, Smith EB, Maltenfort M, Chen AF, Parvizi J. Aspirin Can Be Used as Prophylaxis for Prevention of Venous Thromboembolism After Revision Hip and Knee Arthroplasty. J Arthroplasty. 2016;31(10):2237-2240.
129. Faour M, Piuzzi NS, Brigati DP, et al. Low-Dose Aspirin Is Safe and Effective for Venous Thromboembolism Prophylaxis Following Total Knee Arthroplasty. J Arthroplasty. 2018;33(7S):S131-S135.
130. Taylor SL, Dy S, Foy R, et al. What context features might be important determinants of the effectiveness of patient safety practice interventions? BMJ Qual Saf. 2011;20(7):611-617.
131. Campbell DA, Jr., Thompson M. Patient safety rounds: description of an inexpensive but important strategy to improve the safety culture. Am J Med Qual. 2007;22(1):26-33.
132. Cross T, Bazron B, Dennis K, et al. Towards a Culturally Competent System of Care: AMonograph on Effective Services for Minority Children Who Are Severely Emotionally Disturbed. https://spu.edu/%7E/media/academics/school-of-education/Cultural%20Diversity/Towards%20a%20Culturally%20Competent%20System%20of%20Care%20Abridged.ashx. Accessed October 21, 2021.
133. Office of Minority Health. The National CLAS Standards. https://minorityhealth.hhs.gov/omh/browse.aspx?lvl=2&lvlid=53. Accessed October 21, 2021.
134. Divi C, Koss RG, Schmaltz SP, Loeb JM. Language proficiency and adverse events in US hospitals: a pilot study. Int J Qual Health Care. 2007;19(2):60-67.
135. Saha S, Korthuis PT, Cohn JA, Sharp VL, Moore RD, Beach MC. Primary care provider cultural competence and racial disparities in HIV care and outcomes. J Gen Intern Med. 2013;28(5):622-629.
136. DeCamp LR, Kuo DZ, Flores G, O'Connor K, Minkovitz CS. Changes in language services use by US pediatricians. Pediatrics. 2013;132(2):e396-406.
137. King HM, Batles J, Baker DP, et al. TeamSTEPPS™: Team Strategies and Tools To Enhance Performance and Patient Safety. Advances in Patient Safety: New Directions and Alternative Approaches (Vol 3: Performance and Tools). https://www.ncbi.nlm.nih.gov/books/NBK43686/. Accessed October 21, 2021.
138. Weaver SJ, Dy SM, Rosen MA. Team-training in healthcare: a narrative synthesis of the literature. BMJ Qual Saf. 2014;23(5):359-372.

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.

LEARNER RECORDS: SAMPLE

To Receive Credit: Please ensure information entered matches the information on file with the Kentucky Board of Medical Licensure. Please write legibly, failure to accurately provide this information may result in your data being non-reportable. Using the spaces provided below, please PRINT the information below in CAPITAL LETTERS. Upon completion, please place this sheet in the envelope provided and mail to the address above. If paying by check or money order, please make payable to InforMed. For even faster service, we offer this test online with instant grading and certificate issuance online at **BOOK.CME.EDU**

Please PRINT NEATLY in the areas below using black or blue pen only:

First Name: JOHN | MI.: F | Last Name: DOE

Mailing Address: 123 CHEERY STREET

Suite / Floor / Apt. Number: 456 | City (do not abbreviate): LOUISVILLE | State: KY

Zip Code: 40222 | Telephone Number: 919-456-7890 | Kentucky Medical License#: 45678

E-mail address (Include to receive processing confirmation and instant certificate access): JOHNDOE@EMAIL.COM

Required Information for MOC Reporting (if desired)

Specialty Board: ABIM (ABA, ABIM, ABO, ABOHNS, ABPath, ABP) | ID Number: 123456 | License Type: MD (MD, DO, PA, etc.) | Date of Birth (mm/dd/yyyy): 12/21/1980

LICENSE NUMBER FORMATS:

<u>Doctor of Medicine (MD) & Doctor of Osteopathic Medicine (DO):</u>
3-5 digits
(Ex: 15678)

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
PO Box 2595 | Ormond Beach, FL 32175

2023 Kentucky Medical Licensure Program

Learner Records: Answer Sheet and Payment Information

To Receive Credit: Please ensure information entered matches the information on file with the Kentucky Board of Medical Licensure. Please write legibly, failure to accurately provide this information may result in your data being non-reportable. Using the spaces provided below, please PRINT the information below in CAPITAL LETTERS. Upon completion, please place this sheet in the envelope provided and mail to the address above. If paying by check or money order, please make payable to InforMed. For even faster service, we offer this test online with instant grading and certificate issuance online at **BOOK.CME.EDU**

Please PRINT NEATLY in the areas below using black or blue pen only:

First Name | MI. | Last Name

Mailing Address

Suite / Floor / Apt. Number | City (do not abbreviate) | State

Zip Code | Telephone Number | Kentucky Medical License#

E-mail address (Include to receive processing confirmation and instant certificate access)

Required Information for MOC Reporting (if desired)

Specialty Board (ABA. ABIM. ABO. ABOHNS. ABPath. ABP) | ID Number | License Type (MD, DO, PA, etc.) | Date of Birth (mm/dd/yyyy)

Payment Method

☐ Check / M.O. Enclosed
☐ Credit Card

☐ Entire Program $75.00
☐ Courses 1 & 2 $55.00

Visa / Mastercard / AMEX / Discover Number | Credit Card Expiration Date | Security Code

Cardholder Signature: _____

Shade circles like this: ● Final exam questions are located at the end of each chapter.

Effective Management of Acute and Chronic Pain with Opioid Analgesics

	A	B	C	D
1	○	○	○	○
2	○	○	○	○
3	○	○	○	○
4	○	○	○	○
5	○	○	○	○
6	○	○	○	○
7	○	○	○	○
8	○	○	○	○
9	○	○	○	○
10	○	○	○	○

Alternatives to Opioids for Pain Management

	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	○	○	○	○

For Internal Use Only - Do Not Mark In This Area

KY23CME

5079645691

Book expires: 9/30/2024 Program. KY23CME Courses 1 & 2. KY23CME-55 Course 1. KY23CME-50 Course 2. KY23CME-30 Course 3. KY23CME-80

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 - EFFECTIVE MANAGEMENT OF ACUTE AND CHRONIC PAIN WITH OPIOID ANALGESICS:

		A	B	C	D
1.	Assess non-pharmacological, non-opioid, and opioid analgesic therapies in comprehensive pain plans for patients with acute or chronic pain.	○	○	○	○
2.	Identify and manage patients with opioid use disorder and recognize when to incorporate emergency opioid antagonists into prescribing practice.	○	○	○	○

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 - ALTERNATIVES TO OPIOIDS FOR PAIN MANAGEMENT:

		A	B	C	D
5.	Utilize a function-based paradigm for creating treatment plans for chronic pain conditions and follow guideline-recommended steps for initiating treatments for acute and chronic pain conditions.	○	○	○	○
6.	Appropriately prescribe the full range of non-opioid analgesic options for managing acute and chronic non-cancer pain	○	○	○	○

7. Please identify a specific change, if any, you will make in your practice related to alternatives to opioids for pain management. _____

_____

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

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, e-mail 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.

Fastest way to receive your certificate of completion

Online

- Go to **BOOK.CME.EDU**. Locate the book code **KY23CME** 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	Credits	Code	Price
Entire Program	17	KY23CME	$75.00
Courses 1 & 2	5	KY23CME-55	$55.00

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 e-mail 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.

InforMed
Continuing Medical Education
By Colibri Healthcare
P.O. Box 2595 | Ormond Beach, FL 32175-2595

BOOK CODE: KY23CME
BOOK EXPIRES: 9/30/2024

Current Three-Year CME Cycle:
January 1, 2021 - December 31, 2023

2023 Kentucky Medical Licensure Program

- **4.5 HOURS**
  HB 1 / Pain Management / Addiction / KASPER*

ACCME ACCREDITED

***Physician CME Requirement:**
Four and one-half (4.5) credits relating to the use of KASPER, pain management, addiction disorders or a combination of two or more in these content areas.

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

KYPHY.CME.EDU

ACCME ACCREDITED

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