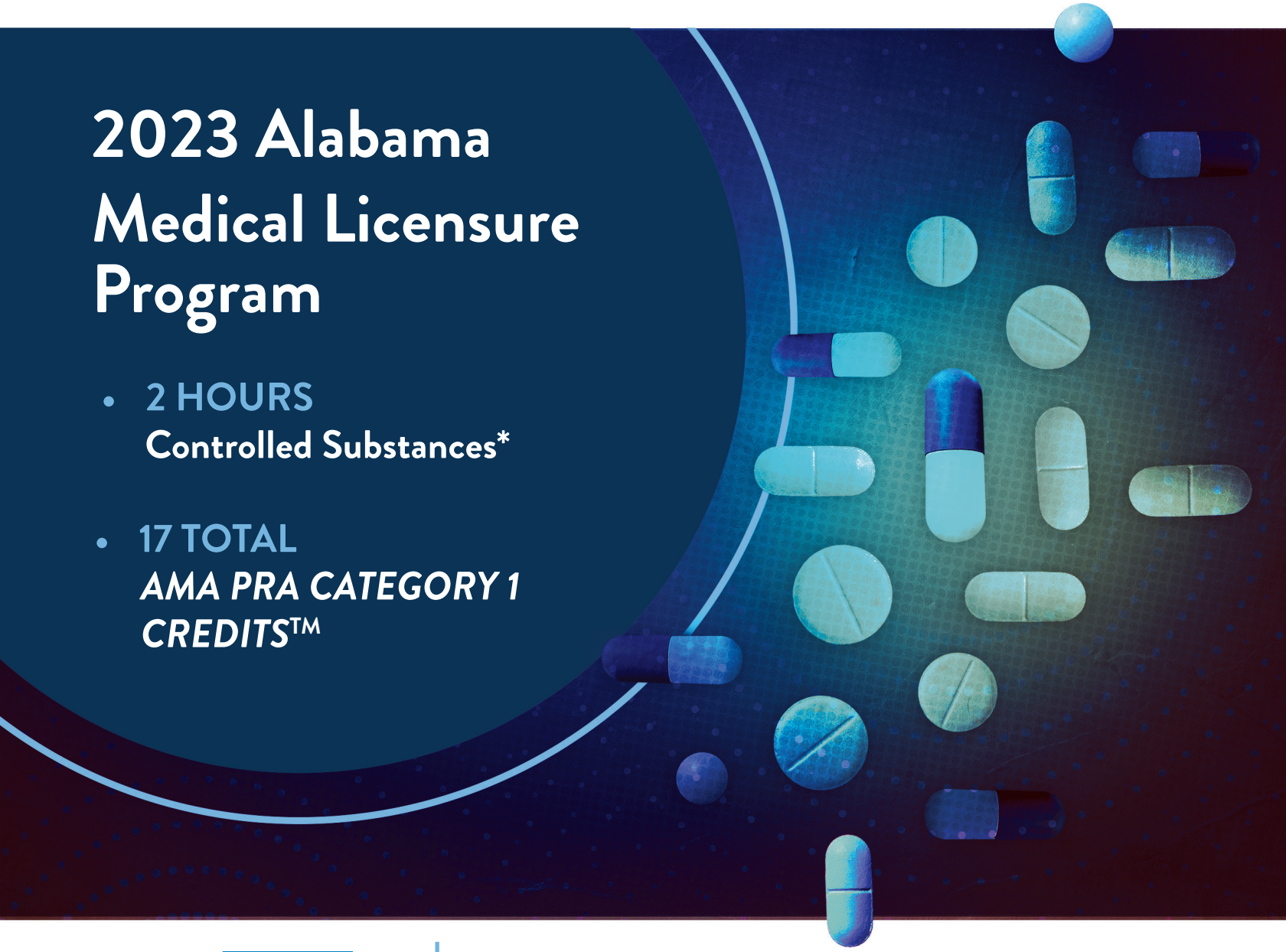
InforMed
Continuing Medical Education
By Colibri Healthcare

State Specific Continuing Medical Education

2023 Alabama Medical Licensure Program



- 2 HOURS
  Controlled Substances*
- 17 TOTAL
  AMA PRA CATEGORY 1 CREDITS™

ACCME ACCREDITED

*Physician CME Requirement:

2 Credits on prescribing and monitoring of controlled substances

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

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2023 ALABAMA

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REQUIRED TO RECEIVE CREDIT

***Either offered course fulfills the required two (2) credits on controlled substance prescribing for Physicians (MD/DO) with an Alabama Controlled Substance Certificate (ACSC).**

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	$55.00
ENTIRE PROGRAM	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.

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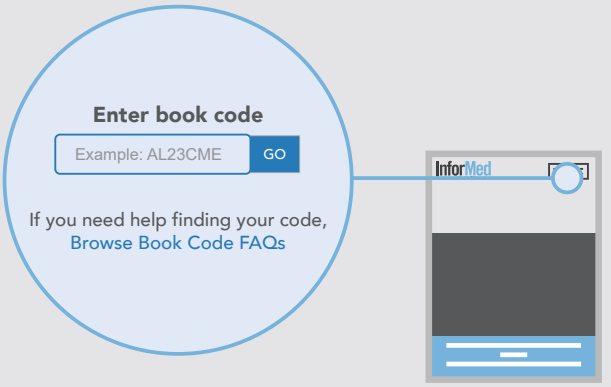
- Follow the online instructions to complete your self-assessment. Complete the purchase process to receive course credit and your certificate of completion. Please remember to complete the online evaluation.



Program Options	Credits	Code	Price
Entire Program	17	AL23CME	$75.00
Courses 1 & 2	5	AL23CME-55	$55.00
Course 1	2	AL23CME-50	$50.00

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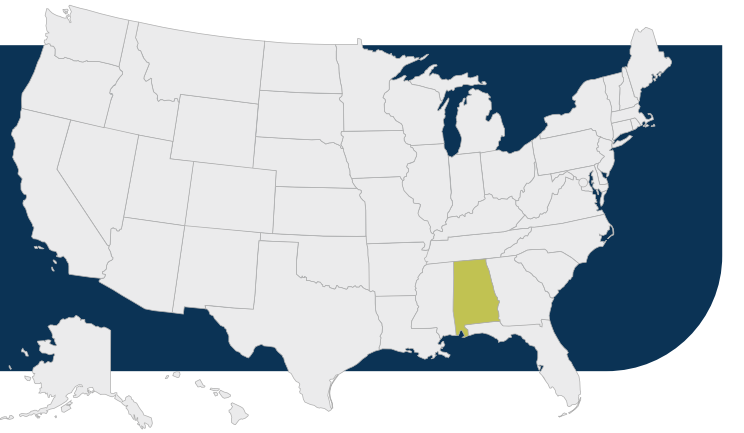
- Fill out the answer sheet and evaluation found in the back of this booklet. Please include credit card information and e-mail address. Fax to **1-800-647-1356**.
- All completions will be processed within 2 business days of receipt and certificates will be e-mailed to the address provided.
- Submissions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

INFORMED TRACKS
WHAT YOU NEED, WHEN YOU NEED IT



Alabama Professional License Requirements

MINIMUM CONTINUING MEDICAL EDUCATION REQUIREMENTS FOR RENEWAL

PHYSICIANS (MD/DO)

Every Physician (MD/DO) licensed to practice medicine in Alabama must earn twenty-five (25) *AMA PRA Category 1 Credits*™ or equivalent of continuing medical education each calendar year, on or before December 31st, unless he or she is exempt from the minimum requirement. For more information on the minimum CME requirements visit http://www.albme.org/cme.html.

MANDATORY CONTROLLED SUBSTANCES CME

Physicians (MD/DO) with an Alabama Controlled Substance Certificate (ACSC)

Each holder of a ACSC shall acquire two (2) *AMA PRA Category 1 Credits*™ on controlled substance prescribing every two (2) years as part of the licensee's yearly CME requirement. The controlled substance prescribing education shall include instruction on controlled substance prescribing practices, recognizing signs of the abuse or misuse of controlled substances, or controlled substance prescribing for chronic pain management.

For more information on the mandatory controlled substances CME for ACSC holders, visit http://www.albme.org/cscme.html.

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

Alabama Board of Medical Examiners
Post Office Box 946
Montgomery, Alabama 36101-0946
P: (334) 242-4116

END OF CURRENT CME CYCLE:
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**
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
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
Understanding and Compassion: Pain, Addiction and End-of-Life Care	12 *AMA PRA Category 1 Credits*™	12 Credits LL	12 Credits MK	12 Credits LL & SA	12 Credits SA	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.

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 on 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.

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COURSE SATISFIES

SPECIAL DESIGNATION

This course satisfies two (2) *AMA PRA Category 1 Credits*™ on controlled substance prescribing.

Physicians (MD/DO) with an ACSC must complete two (2) *AMA PRA Category 1 Credits*™ on controlled substance prescribing every two years.

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.

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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.

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ALTERNATIVES TO OPIOIDS FOR PAIN MANAGEMENT

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. 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.

2. 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.

3. 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.

4. 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.

5. 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.

6. 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.

7. 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.

8. 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.

9. 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.

10. 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

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.

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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.

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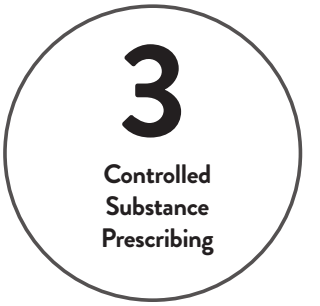

SPECIAL DESIGNATION

This course satisfies three (3) *AMA PRA Category 1 Credits*™ on controlled substance prescribing.

Physicians (MD/DO) with an ACSC must complete two (2) *AMA PRA Category 1 Credits*™ on controlled substance prescribing every two years.

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:

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

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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).

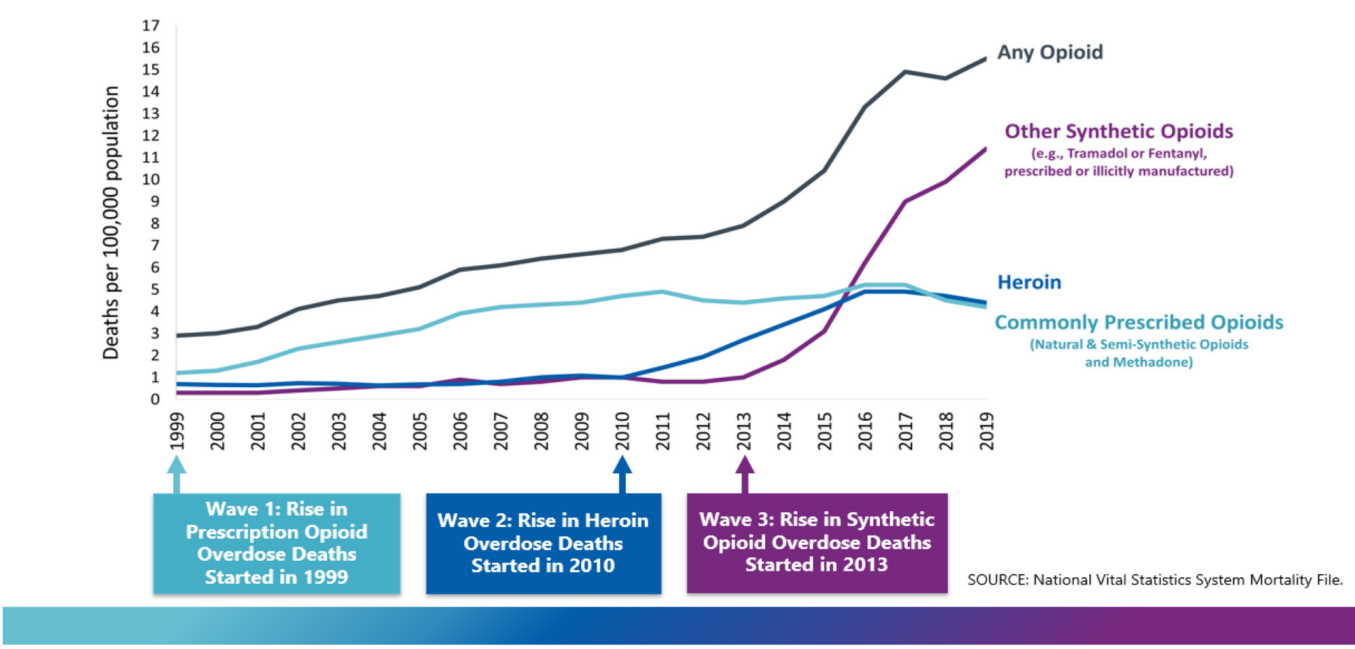
Semi-synthetic opioids: analgesics containing both natural and manufactured compounds (e.g., oxycodone, hydrocodone, hydromorphone, oxymorphone).

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.

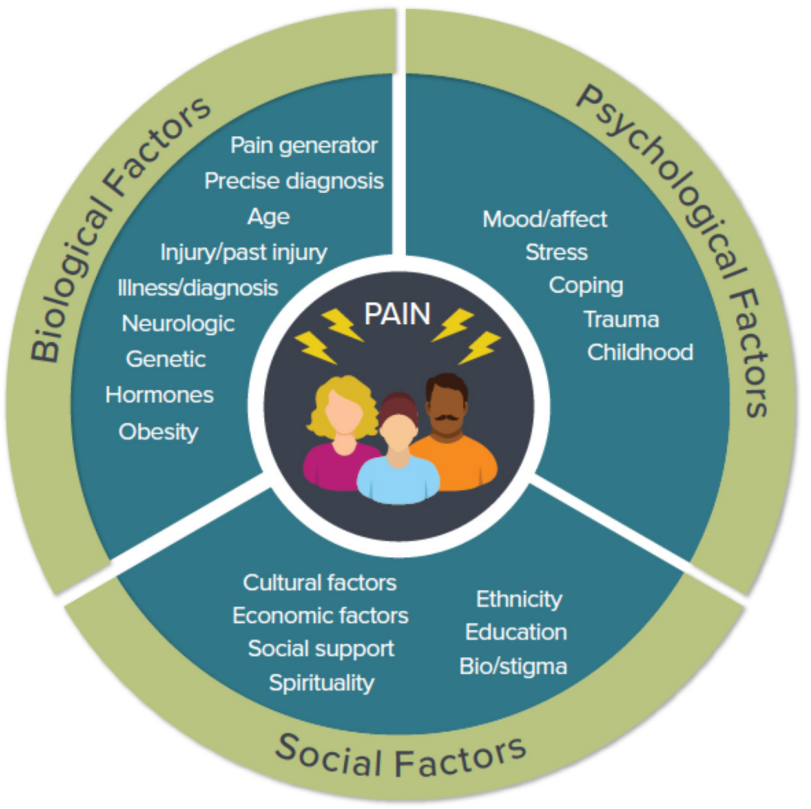
Evaluating pain

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]

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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?**

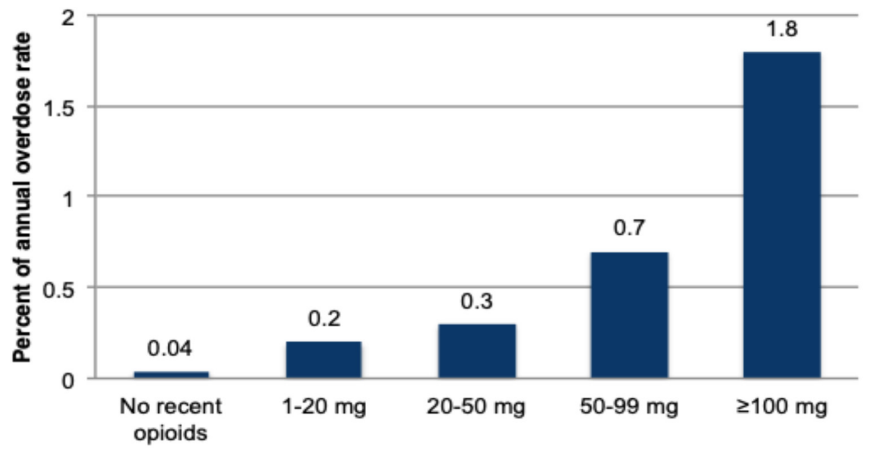
3. **Would Wayne's current medication need to be adjusted if he were to be prescribed an ER/LA opioid?**

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.

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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.

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Self-Assessment

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

11. 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.

12. 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.

13. 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.

14. 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.

15. 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.

16. 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.

17. 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.

18. 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.

19. 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.

20. 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

UNDERSTANDING AND COMPASSION: PAIN, ADDICTION AND END-OF-LIFE CARE

COURSE DATES:	MAXIMUM CREDITS:	FORMAT:
Release Date: 1/2023 Exp. Date: 12/2025	12 *AMA PRA Category 1 Credits*™	Enduring Material (Self Study)

TARGET AUDIENCE

This course is designed for all physicians (MD/DO), physician assistants, nurse practitioners and other healthcare professionals who seek to improve palliative care, pain management, and addiction for their patients.

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

Physicians and other healthcare professionals are constantly striving to improve care for patients. Certain disease states can present challenging circumstances for the physician to manage: addiction, effective management of painful conditions, and care at the end of life care. This educational activity addresses each of these complicated concerns and examines many tools available to physicians to compassionately and appropriately care for patients experiencing these afflictions.

LEARNING OBJECTIVES

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

1. Explain general trends in the preferences that patients typically have for care at the end of life.
2. Discuss the appropriate role of physicians in managing patients in hospice programs.
3. Describe the advantages and the disadvantages of opioid pain medications in the context of end-of-life pain management.
4. Describe evaluation tools and treatment options for patients in pain.
5. Summarize non-pharmacological treatment modalities for pain.
6. Explain the use of non-opioid treatments for patients in pain.
7. Discuss the use of opioids for the treatment of pain.
8. Describe pain management considerations for terminally ill patients.
9. Summarize the causes of addiction and diagnosis of substance use disorders.
10. Discuss the treatment of opioid use disorder, including medically supervised withdrawal, medication-assisted treatment, and overdose management.
11. Review the risk factors, assessment, and treatment of benzodiazepine use disorder.
12. Explain the effects of alcohol on the body as well as screening for and treatment of alcohol withdrawal and alcohol use disorder.

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

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DISCLAIMER

Introduction to Palliative/End-of-Life Care

In the United States, dying at home in the care of family—the norm for centuries—has been largely replaced by death in hospitals, nursing homes, and other institutions, often with highly technological care delivered by specialist health providers. Although not without benefits, this process of dying can result in isolation of the patient from their loved ones, as well as isolation from familiar and comforting surroundings.

Because Americans, on average, live much longer now than they did in the past, a much larger proportion of the population dies at an advanced age. More than 70 percent of those who die each year are age 65 or over, and those who die in old age tend to die of different causes than those who die young.[1] The dying process today tends to be more extended, in part because medical treatments can manage pneumonia, infections, kidney failure, and other immediate causes of death that come in the wake of cancer or chronic disease.

The field of palliative care is one response to the changing profile of death in the 21st century. It focuses on the prevention and relief of suffering by carefully managing symptoms and by paying close attention to the emotional, spiritual, and practical needs of patients and those close to them. Other community and professional responses include the development of hospice programs, bereavement support groups, and policies and programs that encourage communication about people's goals and preferences as they approach death.

Palliative care is both a general approach to patient care (integrated with disease-modifying therapies) as well as a growing practice specialty. Primary care physicians are often expected to provide basic elements of palliative care (e.g., pain and symptom assessment and management, advance care planning), but complex cases may be best handled by palliative care specialists.

Decisions about the use of life-sustaining treatment when a person is seriously ill or near death have profound consequences for that person, for his or her family and loved ones, and, often, for health care providers. Such decisions may determine the time and circumstances of the person's death and may shape the person's experience of remaining life—where it is lived, with whom, and with what degree of comfort or suffering. Physicians thus have a compelling responsibility to be as compassionate and competent in their care of dying patients as with patients at any other phase of their lives.

Unfortunately, the education and training of physicians and other health care professionals often fail to provide them the attitudes, knowledge, and skills required to care well for the dying patient.[2]

Many deficiencies in practice stem from fundamental insufficiencies in professional education. Undergraduate, graduate, and continuing education programs often do not sufficiently prepare health professionals to recognize the final phases of illnesses, to understand and manage their own emotional reactions to death and dying, to construct effective strategies for care, and to communicate sensitively with patients and those close to them.

This CME learning activity summarizes the major dimensions of end-of-life (EOL) care that clinicians are likely to encounter as they care for, and comfort, patients in their final phase of life.

Patient preferences for EOL care

Predicting what treatments patients will want at the end of life is complicated by factors such as the patient's age, the nature of the illness, the ability of medicine to sustain life, and the emotions families endure when a loved one is sick or dying. When seriously ill patients are nearing the end of life, they and their families sometimes find it difficult to decide whether to continue medical treatment and, if so, how much treatment and for how long. In these instances, patients rely on their physicians or other trusted health professionals for guidance.

In the best circumstances, the patient, the family, and the physician have discussed treatment options, including the length and invasiveness of treatment, chances of success, overall prognosis, and the patient's quality of life during and after the treatment. Ideally, these conversations would continue as the patient's condition changes. Frequently, however, such discussions are not held. If the patient becomes incapacitated due to illness, the patient's family and physician must make decisions based on what they think the patient would want.

While no one can predict exactly what patients will want or need when they are sick or dying, current research can help providers offer end-of-life care based on preferences (both real and hypothetical) held by the majority of patients under similar circumstances.[3] Research indicates that most patients have not participated in advance care planning, yet many are willing to discuss end-of-life care. One way to determine patients' preferences for end-of-life care is to discuss hypothetical situations and find out their opinions on certain treatment patterns. These opinions can help clarify and predict the preferences they would be likely to have it if they should become incapacitated and unable to make their own decisions.

The Patient Self-Determination Act guarantees patients the right to accept or refuse treatment and to complete advance medical directives.[4]

However, despite patients' rights to determine their future care, research reveals that:[3,5]

- Only one in three American adults have created an advance directive expressing their wishes for end-of-life care.
- 28% of home healthcare patients, 65% of nursing home residents, and 88% of hospice care patients have created advance directives.
- Only 12 percent of patients with an advance directive received input from their physician in its development.
- As many as three-quarters of physicians whose patients had an advance directive were not aware that it existed.
- Having an advance directive did not increase documentation in the medical chart regarding patient preferences.
- Advance directives helped make end-of-life decisions in less than half of the cases where a directive existed.
- Advance directives usually were not applicable until the patient became incapacitated and "absolutely, hopelessly ill."
- Providers and patient surrogates had difficulty knowing when to stop treatment and often waited until the patient was actively dying before the advance directive was invoked.
- Language in advance directives was usually too vague and general to provide clear instruction.
- Surrogates named in the advance directive often were not present to make decisions or were too emotionally distraught to offer guidance.
- Physicians were only about 65 percent accurate in predicting patient preferences and tended to make errors of under-treatment, even after reviewing the patient's advance directive.
- Surrogates who were family members tended to make prediction errors of overtreatment, even if they had reviewed or discussed the advance directive with the patient or assisted in its development.

Research also shows that care at the end of life is sometimes inconsistent with the patients' preferences to forgo life-sustaining treatment, and that patients may receive care they do not want. For example, one study found that patient preferences to decline cardiopulmonary resuscitation (CPR) were not translated into do-not-resuscitate (DNR) orders.[6] Another study found that patients received life-sustaining treatment at the same rate regardless of their desire to limit treatment.[7]

Because physicians are in the best position to know when to bring up the subject of end-of-life care, they are the ones who need to initiate and guide advance care planning discussions.

Such discussions are usually reserved for people who are terminally ill or whose death is imminent, yet research indicates that people suffering from chronic illness also need advance care planning. Most people who die in the United States (80 to 85 percent) are Medicare beneficiaries age 65 and over, and most die from chronic conditions such as heart disease, cancer, chronic lower respiratory diseases, stroke, diabetes, Alzheimer's disease, and renal failure.[8]

Only about 22 percent of deaths in people age 65+ are from cancer, which generally follows an expected course, or "trajectory," leading to death.[8] Many maintain their activities of daily living until about 2 months prior to death, after which most functional disability occurs. In contrast, people with chronic diseases such as heart disease or COPD go through periods of slowly declining health marked by sudden severe episodes of illness requiring hospitalization, from which the patient recovers.

This pattern may repeat itself, with the patient's overall health steadily declining, until the patient dies. For these individuals there is considerable uncertainty about when death is likely to occur. Patients who suffer from chronic conditions such as stroke, dementia, or the frailty of old age go through a third trajectory of dying, marked by a steady decline in mental and physical ability that finally results in death. Patients are not often told that their chronic disease is terminal, and estimating a time of death for people suffering from chronic conditions is much more difficult than it is for those dying of cancer.

When patients are hospitalized for health crises resulting from their chronic incurable disease, medical treatment cannot cure the underlying illness, but it is still effective in resolving the immediate emergency and thus possibly extending the patient's life. At any one of these crises the patient may be close to death, yet there often is no clearly recognizable threshold between being very ill and actually dying.

Patients value advance care planning discussion

According to patients who are dying and their families who survive them, lack of communication with physicians and other health care providers causes confusion about medical treatments, conditions and prognoses, and the choices that patients and their families need to make.[2] One study indicated that about one-third of patients would discuss advance care planning if the physician brought up the subject and about one-fourth of patients had been under the impression that advance care planning was only for people who were very ill or very old.[9] Only 5 percent of patients in this study stated that they found discussions about advance care planning too difficult. Other studies have shown that discussing advance care planning and directives with their doctor increased patient satisfaction among patients age 65 years and over.[10]

Patients who talked with their families or physicians about their preferences for end-of-life care had less fear and anxiety, felt they had more ability to influence and direct their medical care, believed that their physicians had a better understanding of their wishes, and indicated a greater understanding and comfort level than they had before the discussion. Compared to surrogates of patients who did not have an advance directive, surrogates of patients with an advance directive who had discussed its content with the patient reported greater understanding, better confidence in their ability to predict the patient's preferences, and a stronger belief in the importance of having an advance directive.

Finally, patients who had advance planning discussions with their physicians continued to discuss and talk about these concerns with their families. Such discussions enabled patients and families to reconcile their differences about end-of-life care and could help the family and physician come to agreement if they should need to make decisions for the patient.

Opportunities for advance planning discussions

Research indicates that physicians can conduct advance care planning discussions with many patients during routine outpatient office visits. Hospitalization for a serious and progressive illness offers another opportunity. The Patient Self-Determination Act requires facilities such as hospitals that accept Medicare and Medicaid money to provide written information to all patients concerning their rights to refuse or accept treatment and to complete advance directives. Patients often send cues to their physicians that they are ready to discuss end-of-life care by talking about wanting to die or asking about hospice. Certain situations, such as approaching death or discussions about prognoses or treatment options that have poor outcomes, also lend themselves to advance care planning discussions. Predicting when patients are near death is difficult, but providers can ask themselves the question: are the patients "sick enough today that it would not be surprising to find that they had died within the next year (or few months, or 6 months)"?

A five-part process has been suggested to guide structured discussions about end-of-life care:[2]

1. **Initiate a guided discussion.** During this discussion, the physicians should share their medical knowledge of hypothetical scenarios and treatments applicable to a patient's particular situation and find out the patient's preferences for providing or withholding treatments under certain situations. The hypothetical scenarios should cover a range of possible prognoses and any disability that could result from treatment. By presenting various hypothetical scenarios and probable treatments and noting when the patient's preferences change from "treat" to "do not treat," the physician can begin to identify the patient's personal preferences and values.
   The physician can also determine if the patient has an adequate understanding of the scenario, the treatment, and possible outcomes. One study indicated that elderly patients have enough knowledge about advance directives, CPR, and artificial nutrition/hydration on which to base decisions for treatment at the end of life, but they do not always understand their realistic chances for a positive outcome.[11] Other research indicates that patients significantly overestimate their probability of survival after receiving CPR and have little or no understanding of mechanical ventilation.[12] After patients were told their probability of survival, over half changed their treatment preference from wanting CPR to refusing CPR. Patients also may not know of the risks associated with the use of mechanical ventilation, such as neurological impairment or cardiac arrest.
2. **Introduce the subject of advance care planning and offer information.** Patients should be encouraged to complete both an advance directive and durable power of attorney. The patient should understand that when no advance directive or durable power of attorney exists, patients essentially leave treatment decisions to their physicians and family members. Physicians can provide this information themselves; refer the patient to other educational sources, including brochures or videos; or recommend that the patient talk with clergy or a social worker to answer questions or address concerns.
3. **Prepare and complete advance care planning documents.** Advance care planning documents should contain specific instructions. The standard language contained in advance directives often is not specific enough to be effective in directing care. Many times, instructions do not state the cutoff point of the patient's illness that should be used to discontinue treatment and allow the person to die. Terms such as "no advanced life support" are too vague to guide specific treatments. If a patient does not want to be on a ventilator, the physician should ask the patient if this is true under all circumstances or only specific circumstances.
4. **Review the patient's preferences on a regular basis and update documentation.** Patients should be reminded that advance directives can be revised at any time. Although studies show that patient preferences are stable over time when considering hypothetical situations, patients often change their minds when confronted with an actual situation or as their health status changes.[13] Some patients who stated that they would rather die than endure a certain condition did not choose death once that condition occurred. Other research shows that patients who had an advance directive maintained stable treatment preferences 86 percent of the time over a 2-year period, while patients who did not have an advance directive changed their preferences 59 percent of the time.[14] Both patients with and without a living will were more likely to change their preferences and desire increased treatment once they became hospitalized, suffered an accident, became depressed, or lost functional ability or social activity. Another study linked changes in depression to changes in preferences for CPR.[15] Increased depression was associated with patients' changing their initial preference for CPR to refusal of CPR, while less depression was associated with patients' changing their preference from refusal of CPR to acceptance of CPR. It is difficult for people to fully imagine what a prospective health state might be like. Once they experience that health state, they may find it more or less tolerable than they imagined.

During reviews of advance directives, physicians should note which preferences stay the same and which change. Preferences that change indicate that the physician needs to investigate the basis for the change.

5. **Apply the patient's desires to actual circumstances.** Conflicts sometimes arise during discussions about end-of-life decision-making. If patients desire non-beneficial treatments or refused beneficial treatments, most physicians state that they would negotiate with them and try to educate and convince them to either forgo a non-beneficial treatment or to accept a beneficial treatment.[16] If the treatment was not harmful, expensive, or complicated, about one-third of physicians would allow the patient to receive a non-beneficial treatment. Physicians stated that they would also enlist the family's help or seek a second opinion from another physician. Many patients do not lose their decision making capacity at the end of life. Physicians and family members can continue discussing treatment preferences with these patients as their condition changes. However, physicians and families may encounter the difficulty of knowing when an advance directive should become applicable for patients who are extremely sick and have lost their decision making capacity but are not necessarily dying. There is no easy answer to this dilemma. Even if patients require a decision for a situation that was not anticipated and addressed in their advance directive, physicians and surrogates still can make an educated determination based on the knowledge they have about the patients' values, goals, and thresholds for treatment.

Legalities of the Advance Directive & POLST:

An advance directive in general is not a legally binding document. While a succinct advance directive can be a description of a patient's wishes, the patient's family is not legally bound to follow it in case of the patient's incapacitation. A Physicians Orders for Life Sustaining Treatment (POLST) which has various names in various states, is in general designed as a legally binding series of medical orders that the patients primary healthcare provider puts in writing after discussion with the patient. This allows for the patient's wishes to be more easily accepted by putting the wishes into a simple to read, standardized for the state form, that carries the weight of physician orders. Each state's rules vary, however generally speaking the POLST can be amended by the signatory or other legally authorized individuals. If planning for a patient's end of life wishes a POLST or similar document is likely a better choice than a typical advance directive. While data about the POLST is generally limited, and focused mostly on Oregon, it is suggested from the current data that there is likely benefit to using a structured form like the POLST. [109]

The importance of shared decision making

Effective patient-provider communication and shared decision making is achieved in part through *active listening, facilitation, and empathetic comments*.[17] These skills lead to an engaged, dynamic relationship between patients, their families, and health care providers. This partnership should be grounded in mutuality, which includes the sharing of information, creation of consensus, and other components of the shared decision making paradigm.[18]

Reflective listening

An effective communication strategy in any patient-physician relationship is *reflective listening*. This means listening carefully and non-judgmentally to what your patient is saying, then reflecting it back in a slightly modified or re-framed manner.[19] This lets the clinician confirm the accuracy of their understanding of the patient and gives the patient both the indication that they are being heard (an all-too-rare experience for many patients with chronic illness) and a chance to correct mistaken beliefs or perceptions that could affect their care.

Using a reflective listening strategy can take practice. If a patient says something at odds with the evidence, for example, or uses threatening or hostile language, one's natural reaction is to immediately defend oneself, rebut the charges, or deny the underlying assumptions. This can quickly create confrontation or a power-struggle that can be difficult to reverse. In these situations it's important to pause before speaking, and then to consciously try to simply re-state what the patient just said. For example, a patient may say, "Doctor, those pills you gave me don't work—I told you before that I need something stronger." A directly confrontational response will probably be ineffective. A better response would be something like "You seem to be irritated with me because you don't think the medications I prescribed are working for you."

In summary, reflective listening techniques provide several advantages:[19]

- They are less likely to evoke or exacerbate patient defensiveness
- They encourage the patient to keep talking and reveal more about their true feelings
- They communicate respect and caring, and encourage a therapeutic alliance
- They open an opportunity for the patient to clarify exactly what he or she means

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

Preference patterns for hypothetical situations

Evidence suggests that patients are more likely to accept treatment for conditions they consider better than death and to refuse treatment for conditions they consider worse than death. Patients also were more likely to accept treatments that were less invasive such as CPR than invasive treatments such as mechanical ventilation (see Table 1). Patients were more likely to accept short-term or simple treatments such as antibiotics than long-term invasive treatments such as permanent tube feeding.

Table 1. Treatment preferences among patients age 64 and over, from most- to least-preferred[21]

Antibiotics
Blood transfusion
Temporary tube feeding
Temporary respirator
Radiation
Amputation
Dialysis
Chemotherapy
Resuscitation
Permanent respirator
Permanent tube feeding

It is telling that physicians, who are in a better position than others to judge the likely value of EOL services, often choose much less aggressive treatments for themselves than they offer to their patients. A study comparing 78 primary care faculty and residents with 831 of their patients found that the physicians were much less likely than the patients to want five of six specific treatments if they were terminally ill.[20] And 59% of the physicians chose "least aggressive" EOL treatment preferences for themselves.

Acceptance or refusal of invasive and noninvasive treatments under certain circumstances can predict what other choices the patient would make under the same or different circumstances. Refusal of noninvasive treatments such as antibiotics strongly predicted that invasive treatments such as major surgery would also be refused. Research also reveals that patients were more likely to refuse treatment under hypothetical conditions as their prognosis became worse. For example, more adults would refuse both invasive and noninvasive treatments for a scenario of dementia with a terminal illness than for dementia only. Adults were also more likely to refuse treatment for a scenario of a persistent vegetative state than for a coma with a chance of recovery. More patients preferred treatment if there was even a slight chance for recovery from a coma or a stroke. Fewer patients would want complicated and invasive treatments if they had a terminal illness. Finally, patients were more likely to want treatment if they would remain cognitively intact rather than impaired.

Case Study 1

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

Janet is an 83-year-old woman with amyotrophic lateral sclerosis (ALS). Her speech has become very slurred, she is having difficulty chewing and swallowing, and has lost 40 pounds over the course of the past 18 months. She has never liked what she calls the "medical establishment," takes no prescription drugs, and prefers natural and alternative methods of dealing with health issues.

Her neurologist and her three grown children are all concerned about her weight loss and growing frailty and have suggested she have a percutaneous endoscopic gastrostomy (PEG) tube placed so she can get more adequate nutrition and hydration. Janet, however, is not cooperating. She has delayed making a decision and appears unwilling to discuss the matter with anybody. She is now sitting in your office, with one of her sons present, and has just replied angrily to your statement that further delays in getting a feeding tube will hasten her death. "What if I don't see the point in continuing to live, doctor?" she says, struggling to enunciate the words. "Has it crossed your mind that I might not enjoy living under these horrible conditions?"

1. **What would be a possible response to Janet's outburst that would employ the technique of reflective listening?**_____

2. **How could you work with Janet to establish a set of care goals that would be appropriate for either course of action (i.e., having, or not having, the PEG placed)?**_____

3. **If Janet refuses the PEG, what steps could you take to make her final weeks more comfortable?**_____

4. **If Janet continues to feel as though her quality of life is not what she'd want to continue with, are there standardized approaches that could help you address her goals of care in a succinct, state-wide applicable document?**_____

Advance planning helps physicians provide care that patients want

Most people will eventually die from chronic conditions. These patients require the same kind of advance care planning as those suffering from predictably terminal conditions such as cancer. Understanding preferences for medical treatment in patients suffering from chronic illness requires that physicians and other health care providers consider patients' concerns about the severity of prospective health states, length and invasiveness of treatments, and prognosis. While predicting what patients might want is difficult, research offers some insights into treatment patterns and preferences under hypothetical situations that can give providers more insight into their patients' desires under similar circumstances. By discussing advance care planning during routine outpatient visits, during hospitalization for exacerbation of illness, or when the patient or physician believes death is near, physicians can improve patient satisfaction with care and provide care at the end of life that is in accordance with the patient's wishes. Suggested components of an individualized approach to EOL care are summarized in Table 2.

Communicating life-altering news

"*The best way to convey meaning is to tell people what the information means to you yourself. And there are three words to do that: "I am worried." They were such simple words, but it wasn't hard to sense how much they communicated. I had given her the facts. But by including the fact that I was worried, I'd not only told her about the seriousness of the situation, I'd told her that I was on her side—I was pulling for her. The words also told her that, although I feared something serious, there remained uncertainties—possibilities for hope within the parameters nature had imposed.*"[22]

--Atul Gawande, MD

Delivering bad or life-altering news to a patient is one of the most difficult tasks physicians encounter.[23] Ultimately, the determination of what is bad news lies not with the physician, but with the person receiving the news. Although classically related to cancer or a terminal diagnosis, bad or serious news may also include information related to diagnosis of a chronic disease (e.g., diabetes mellitus), a life-altering illness (e.g., multiple sclerosis), or an injury leading to a significant change (e.g., a season-ending knee injury). Most of the research into the delivery of bad news, however, has focused on patients with cancer and subsequently applied to the delivery of bad or serious news in non-oncologic settings.

Patients prefer to receive such news in person, with the physician's full attention, and in clear, easy-to-understand language with adequate time for questions. Most patients prefer to know their diagnosis, but the amount of desired details varies among different cultures and by education level, age, and sex. The physician should respect the patient's unique preferences for receiving bad news.

Physicians may experience stress related to providing bad news that extends beyond the actual conversation. For example, physicians may be afraid of eliciting an emotional reaction, being blamed for the bad news, and expressing their emotions during the process. Physicians often withhold information or are overly optimistic regarding prognosis, but this can lead to confusion for patients regarding their condition. There are several algorithms available to help guide the physician in the delivery of bad news, including the SPIKES protocol (see Table 3, pg. 56). Skillful delivery of bad news can provide comfort for the patient and family.

BEFORE MOVING ONTO THE NEXT SECTION, PLEASE COMPLETE CASE STUDY 2 ON PG. 56.

Table 2. Components of individualized EOL care[2]	
Component	**Rationale**
Frequent assessment of the patient's physical, emotional, social, and spiritual well-being	Interventions and care should be based on accurately identified needs.
Management of emotional distress	All clinicians should be able to identify distress and direct its initial and basic management. This is part of the definition of palliative care, a basic component of hospice, and clearly of fundamental importance.
Offer referral to expert-level palliative care	People with palliative needs beyond those that can be provided by non-specialist-level clinicians deserve access to appropriate expert-level care.
Offer referral to hospice if the patient has a prognosis < 6 months.	People who meet the hospice eligibility criteria deserve access to services designed to meet their end-of-life needs.
Management of care and direct contact with patient and family for complex situations by a specialist level palliative care physician	Care of people with serious illness may require specialist-level palliative care physician management, and effective physician management requires direct examination, contact, and communication.
Round-the-clock access to coordinated care and services	Patients in advanced stages of serious illness often require assistance, such as with activities of daily living, medication management, wound care, physical comfort, and psychosocial needs. Round-the-clock access to a consistent point of contact that can coordinate care obviates the need to dial 911 and engage emergency medical services.
Management of pain and other symptoms	All clinicians should be able to identify and direct the initial and basic management of pain and other symptoms. This is part of the definition of palliative care, a basic component of hospice, and clearly of fundamental importance.
Counseling of patient and family	Even patients who are not emotionally distressed face problems in such areas as loss of functioning, prognosis, coping with diverse symptoms, finances, and family dynamics, and family members experience these problems as well, both directly and indirectly.
Family caregiver support	A focus on the family is part of the definition of palliative care; family members and caregivers both participate in the patient's care and require assistance themselves.
Attention to the patient's social context and social needs	Person-centered care requires awareness of patients' perspectives on their social environment and of their needs for social support, including at the time of death. Companionship at the bedside at time of death may be an important part of the psychological, social, and spiritual aspects of end-of-life care for some individuals.
Attention to the patient's spiritual and religious needs	The final phase of life often has a spiritual and religious component, and research shows that spiritual assistance is associated with quality of care.
Regular personalized revision of the care plan and access to services based on the changing needs of the patient and family	Care must be person-centered and fit current circumstances, which may mean that not all the above components will be important or desirable in all cases.

Culturally Sensitive Communication

Communicating effectively with both patients and their loved ones requires an awareness of some of the cultural differences that can create unexpected barriers or misunderstandings. End-of-life discussions are particularly challenging because of their emotional and interpersonal intensity. Many physicians are unfamiliar with common cultural variations regarding physician-patient communication, medical decision making, and attitudes about formal documents such as code status guidelines and advance directives.[25]

Although cultural differences certainly exist, generalizations about specific cultures are not always applicable to specific patients because there is wide variation in the ways that individuals adhere or adopt the stereotypical beliefs, values, or attitudes of a particular culture. In fact, research suggests that when compared with whites of European descent, ethnic minorities exhibit greater variability in their cultural beliefs and preferences.[26]

Clinicians should be aware that different cultures may place different emphasis—or disagree completely—with principles of medical conduct that they take for granted. For example, in the United States, legal documents such as advance directives and durable powers of attorney are strategies to prolong autonomy in situations in which patients can no longer represent themselves. Other cultures, however, de-emphasize autonomy, perceiving it as isolating rather than empowering. These non-Western cultures believe that communities and families, not individuals alone, are affected by life-threatening illnesses and the accompanying medical decisions.[27]

Cultures valuing non-malfeasance (doing no harm) may try to protect patients from the emotional and physical harm caused by directly addressing death and end-of-life care. Many Asian and Native American cultures value beneficence (physicians' obligation to promote patient welfare) by encouraging patient hope, even in the face of terminal illness. Patient or family member preferences for nondisclosure of medical information and family-centered decision making may also be surprising to American-trained physicians.

Physicians may improve their rapport with ethnically diverse patients simply by showing interest in their cultural heritage, and more importantly, in each individual's respective approach to both suboptimal news, and approach to death and dying.

Here are some example questions and situations that reflect a culturally sensitive approach to patient interactions:[25]

"Some people want to know everything about their medical condition, and others do not. What is your preference?"

"Do you prefer to make medical decisions about future tests or treatments for yourself, or would you prefer that someone else make them for you?"

To patients who request that the physician discuss their condition with family members: "Would you be more comfortable if I spoke with your (brother, son, daughter) alone, or would you like to be present?" If the patient chooses not to be present: "If you change your mind at any point and would like more information, please let me know. I will answer any questions you have.

Table 3. SPIKES protocol for delivering life-altering news[24]		
Step	**Key Points**	**Example Phrases**
Setting	Arrange for a private room or area. Have tissues available. Limit interruptions and silence electronics. Allow the patient to dress (if after examination). Maintain eye contact (defer charting). Include family or friends as patient desires.	"Before we review the results, is there anyone else you would like to be here?" "Would it be okay if I sat on the edge of your bed?"
Perception	Use open-ended questions to determine the patient's understanding. Correct misinformation and misunderstandings. Identify wishful thinking, unrealistic expectations, and denial.	"When you felt the lump in your breast, what was your first thought?" "What is your understanding of your test results thus far?"
Invitation	Determine how much information and detail a patient desires. Ask permission to give results so that the patient can control the conversation. If the patient declines, offer to meet him or her again in the future when he or she is ready (or when family is available).	"Would it be okay if I give you those test results now?" "Are you someone who likes to know all of the details, or would you prefer that I focus on the most important result?"
Knowledge	Briefly summarize events leading up to this point. Provide a warning statement to help lessen the shock and facilitate understanding, although some studies suggest that not all patients prefer to receive a warning. Use nonmedical terms and avoid jargon. Stop often to confirm understanding.	"Before I get to the results, I'd like to summarize so that we are all on the same page." "Unfortunately, the test results are worse than we initially hoped." "I know this is a lot of information; what questions do you have so far?"
Emotions	Stop and address emotions as they arise. Use empathic statements to recognize the patient's emotion. Validate responses to help the patient realize his or her feelings are important. Ask exploratory questions to help understand when the emotions are not clear.	"I can see this is not the news you were expecting." "Yes, I can understand why you felt that way." "Could you tell me more about what concerns you?"
Strategy and summary	Summarize the news to facilitate understanding. Set a plan for follow-up (referrals, further tests, treatment options). Offer a means of contact if additional questions arise. Avoid saying, "There is nothing more we can do for you." Even if the prognosis is poor, determine and support the patient's goals (e.g., symptom control, social support).	"I know this is all very frightening news, and I'm sure you will think of many more questions. When you do, write them down and we can review them when we meet again." "Even though we cannot cure your cancer, we can provide medications to control your pain and lessen your discomfort."

Case Study 2

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

Terry is the oldest of five siblings. He has been the primary caregiver for his father, Ralph, who is 87 and lives alone following the death of his wife four years previous. Ralph has congestive heart failure, hearing loss, and type 2 diabetes. He was recently admitted to the hospital for pneumonia. While in the hospital, he had a transient ischemic attack, which caused him to become easily confused. Then, possibly due to a micro-stroke, he lost his ability to swallow.

Ralph's attending physician advised the placement of a percutaneous endoscopic gastrostomy (PEG) tube to supply nutrition and hydration. But Ralph had made it clear in his advance directive that he did not want a feeding tube, and he reiterated that desire to Terry. "I'm not afraid to die," he said. "It's time to call it quits."

Terry was torn. Some of his siblings were unhappy with the prospect of refusing the tube placement—they were afraid Ralph would die before they got a chance to see him. But Terry knew his father would fight any efforts to force him to change his mind, and Terry didn't want his last days with his father marred by conflict.

1. **What would be a possible response to Ralph's expression about not being afraid to die that would employ the technique of reflective listening?** _____

2. **How could you work with Ralph to establish a set of care goals that would be appropriate for either course of action (i.e., having, or not having, the PEG placed)?** _____

3. **If Ralph refuses the PEG, what steps could you take to make his final weeks more comfortable?** _____

When discussing medical issues with family members, particularly through a translator, it is often helpful to confirm their understanding: "I want to be sure that I am explaining your mother's treatment options accurately. Could you explain to me your understanding about your mother's condition and the treatment that we are recommending?"

"Is there anything that would be helpful for me to know about your family or religious views about serious illness and treatment?"

"Sometimes people are uncomfortable discussing these issues with a doctor who is of a different race or cultural background. Are you comfortable with me treating you? Will you please let me know if there is anything about your background that would be helpful for me to know in working with you or your (mother, father, sister, brother)?"

The physician's role in managing hospice patients

Hospice is based on the idea that the dying patient has physical, psychological, social, and spiritual aspects of suffering. Hospice is a philosophy, not a specific place, and can be provided in any setting, including patients' homes, nursing homes, and hospitals.[28] Hospice typically involved an interdisciplinary team providing access to a wide range of services to support the primary caregiver, who is responsible for the majority of the patient care. In 2017 about 1.5 million Medicare beneficiaries received hospice care, a 4.5% increase from the previous year and nearly 200,000 more people than used hospice in 2012.[29]

To be eligible for hospice, a patient must have a terminal illness and an estimated prognosis of less than six months. Patients with non-cancer diagnoses (e.g., congestive heart failure, chronic obstructive pulmonary disease, stroke, dementia) currently represent about 70% percent of all hospice decedents.[29] The responsibility for hospice referral in a non-cancer diagnosis often falls to the primary care physician, facilitating continuity of care for the patient in his or her final days and months. In making an appropriate referral, physicians should be aware of some common misconceptions about hospice care (see Table 4).

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Determining prognosis

Deciding whether a patient has a life expectancy < 6 months is an unavoidably imprecise exercise, however the following scales or tools provide clinicians with some quasi-objective criteria to help guide decisions:

- Karnofsky Performance Scale[32]
- National Hospice Organization Medical Guidelines for Determining Prognosis in Selected Non-Cancer Diseases[33]
- Palliative Performance Scale[34]
- Palliative Prognosis Score[35]

Referral patterns

Continuity of care and multigenerational relationships allow a family physician to guide a patient and family through the hospice referral process with a unique knowledge of the patient's values, family issues, and communication style. (In general, most hospice referrals come from physicians, although social workers, nurses, and patients' families can also make a hospice referral.) The majority of caregivers and families of patients who have received hospice care report that they would have welcomed more information about hospice from their primary care physician at the time the diagnosis was labeled terminal.

Most hospices expect the referring physician to remain in charge of the patient's care and to be available by phone or other means for consultation, although expectations for availability vary by hospice. In some cases, the local hospice medical director may be willing to cover the attending physician on weekends and during vacations.

Table 4. Common misconceptions about hospice care[30]

Misconception	Clarification
Patients will be discharged from hospice if they do not die within six months.	There used to be a six-month regulation that penalized hospices and patients when a patient lived too long, but it was revised and there is no longer any penalty for an incorrect prognosis if the disease runs its normal course.
Patients in hospice must have a DNR order.	Medicare does not require a DNR order to enroll in hospice, but it does require that patients pursue palliative, not curative, treatment; individual hospice organizations may require a DNR order before enrolling a patient.
Patients in hospice must have a primary caregiver.	Medicare does not require a primary caregiver, but this may be a requirement of some hospice organizations.
The primary physician must transfer control of his or her patients to hospice.	Most hospice organizations encourage primary physician involvement; the primary physician becomes a part of the team and contributes to the hospice plan of care.
Only patients with cancer are appropriate candidates for hospice.	Anyone with a life expectancy of less than six months and who chooses a palliative care approach is appropriate for hospice.
Only Medicare-eligible patients may enroll in hospice.	Most commercial insurance companies have benefits that mimic the Medicare Hospice Benefit; individual hospices vary in their willingness to take uninsured patients.
Patients in nursing homes are not eligible for hospice.	This was once true, but Medicare now covers patients in nursing homes.
Patients are not eligible for hospice again if they revoke the hospice benefits.	Patients who want to return to hospice care can be readmitted as long as hospice conditions of participation are met.
Only physicians can refer patients to hospice.	Anyone (e.g., nurse, social worker, family member, friend) can refer a patient to hospice.
Hospice care precludes patients from being able to receive chemotherapy, blood transfusions, or radiation.	Medicare requires that hospice must cover all care related to the terminal illness; individual hospice agencies are allowed to determine whether a specific treatment is palliative (providing symptom relief), which will guide what treatments they are willing to cover.
Patients who have elected the hospice benefit can no longer access other health insurance benefits.	Each insurer has rules defining eligibility for covered services; medical problems unrelated to the terminal illness continue to be covered under regular Medicare insurance.
Patients in hospice cannot be admitted to the hospital.	While the patient is enrolled in hospice, most insurance companies, including Medicare, will still cover hospital admissions for unrelated illnesses, as well as for the management of symptoms related to the terminal diagnosis, and respite care.
Hospice care ends when a patient dies.	All hospice programs must provide families with bereavement support for up to one year following the death of the patient.

Case Study 3

Instructions: Spend 5 minutes reviewing the case below and considering the questions that follow. Note: This is an excerpt from an article by Yoojin Na, an emergency room physician at a hospital in metropolitan New York, which appeared in the New York Times.

A woman held her grandfather's hand as he lay in intensive care. The patient in question was in his 90s with progressive dementia and multiple chronic conditions. Since December, he hadn't been able to make it more than a few weeks without a fall. The palliative-care assessment from his last admission gave him an estimated life expectancy of "weeks to months." Everything I saw on examining him told me it was now days. Soon he wouldn't be able to breathe on his own.

I described to his granddaughter the discomfort of having a ventilator pump air into one's lungs. I explained that such measures would only prolong his suffering. Still, she insisted that her grandfather be kept "full code" and have "everything done."

Three days later, the patient went into respiratory distress. Since he was full code, his sudden decline activated a rapid response, which meant all nearby personnel — doctors, nurses, respiratory therapists and techs — rushed to the room to resuscitate him. The inpatient doctor called the family again. This time, they agreed to make his code status D.N.R., for do not resuscitate. But the patient had turned out to have Covid-19, and the family's DNR decision came only after many staff members were exposed reviving him.

He died the next morning.

The whole ordeal made me wonder why people insist on futile care even when it comes at a risk to others.

1. **Why do you think the family initially insisted on having doctors use "full code" procedures for their grandfather?**_____

2. **How would you have handled the conversations with family members when communication was limited to telephones?**_____

3. **If the patient had a POLST, stating they were DNR/DNI, would that have been able to be used to refuse the insistence of full code status by the family, assuming the patient had made the decisions for the POLST? What if it was an advance directive?**_____

In general, the attending physician is expected to be the primary physician of record, be available by telephone or have coverage arranged, write admission orders, and handle the routine decisions for patient care. Some hospices provide attending physicians with standing orders that have broad parameters for the control of common symptoms, such as pain and dyspnea. The attending physician and the hospice medical director are expected to provide certification to Medicare that the patient continues to meet hospice eligibility criteria on a regular basis. The attending physician is also expected to provide medication refills when needed.

Essential drugs for quality care in dying patients

Effective management of symptoms at the end of life is challenging but often can be achieved with fewer than for six key medications. Clinicians can help support patients and family by using these medications judiciously with the assurance that it will provide a death that is as safe, dignified, and comfortable as medically possible. Table 5 summarizes the most common EOL medication classes. Later sections of this activity will explore some of these options in greater detail.

Table 5. Common medications in a "hospice comfort kit"[36]

Medication class	Example medications	Common indications
Antipsychotics	Haloperidol or risperidone	Delirium, agitation
Antipyretics	Acetaminophen (oral or suppository)	Fever
Benzodiazepines	Lorazepam, alprazolam, diazepam	Anxiety, nausea
Opioids	Morphine, oxycodone, hydrocodone	Dyspnea, Nociceptive pain (not generally effective for neuropathic pain)
Secretion medications	Hyoscyamine, atropine	Excessive oropharyngeal secretions
Laxatives	Docusate, lactulose, senna with docusate	Constipation

Pain Management at the End of Life

The following is an overview of the treatment of pain as it applies to the end of life. More detailed information regarding pain management in general will be covered in later sections.

Although pain relief is often considered—and may sometimes be—an end unto itself, it is particularly important for clinicians to recognize that, at the end of life, pain management and control of symptoms may be more appropriately viewed as *means* of achieving the more primary goal of improving or maintaining a patient's overall quality of life. The meaning of "quality of life" varies, not just from patient to patient, but even between the phases of an illness experienced by a single patient. A focus on quality of life is important because sometimes a patient may have priorities that compete with, or supersede, the relief of pain. For example, the end of life can be an extremely important and meaningful time.[37] 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 point is that, at the end of life, decisions about pain relief must be more than usually balanced with a mindful consideration of the patient's own values and desires.

The types of pain syndromes arising at the end of life include most of the acute and chronic pain syndromes clinicians confront in other patients, and many of the same diagnostic and therapeutic strategies and skills are the same or similar. But pain management at the end of life does raise some unique clinical and ethical issues and, hence, these issues are appropriate for a focused consideration. In addition, the prospect of severe, unrelieved pain at the end of life ranks very high among patient fears.

Indeed many people consider the experience of severe pain to be worse than death, which underscores the importance of a thorough clinical understanding this issue.[38]

Managing pain and other symptoms at the end of life is just one component of a wider effort to relieve suffering and help a patient cope with the emotional and psychological aspects of dying.

Nonetheless, a failure to manage pain and other symptoms may make it impossible for the patient to attend to these important dimensions. Uncontrolled pain can push all other priorities aside and sap a person's energy and motivation to focus on potentially positive goals or meaningful experiences. A patient's perception that his or her pain cannot be controlled may also contribute to a broader feeling that he or she has lost control over their lives in general, which can precipitate a downward spiral of depression and/or hopelessness. Effective pain control, on the other hand, not only directly reduces suffering but may allow a patient the energy and positive attitude needed to engage with the emotional and psychological aspects of dying.

Assessing Pain at the End of Life

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, then nonverbal signs or cues must be used to determine if the patient is experiencing pain and to what degree an analgesic approach is effective. In general, even ambiguous signs of discomfort should usually be treated, although caution must be exercised in interpreting such signs.[39] Patients who are actively dying may groan or grunt in ways that suggest they are in pain, although such sounds may, in fact, be the normal expressions attendant to the last moments or hours of life.

Signs of discomfort that are accompanied by more rapid breathing or heart rate should be taken more seriously. Likewise, if physical stimulation of the patient (i.e., during bathing) causes signs of discomfort, increased analgesia may be warranted. Prolonged rapid breathing (> 20/min.) may be uncomfortable because of muscle fatigue and it may therefore be reasonable, even in the absence of other evidence of discomfort, to titrate a pain medication with a target respiratory rate of 15 to 20/minute.[39]

Opioids

Opioid formulations are available in such variety in the US that, typically, a pain regimen can be tailored to each patient.[40] Because there is great variability in how individual patients respond to particular opioid agents, no specific agent is superior to another as first-line therapy. Although morphine was previously considered the "gold standard," it is now recognized that the most appropriate agent is the opioid that works for an individual patient.[41] Morphine and other opioids are generally available in a wide range of formulations and routes of administration, including oral, transmucosal, transdermal, parenteral, and rectal delivery. Both rectal and transdermal routes can be especially valuable at the end of life when the oral route is precluded because of reduced or absent consciousness, difficulty swallowing, or to reduce the chances of nausea and vomiting.[42] When selecting an opioid, clinicians should also consider cost, since expensive agents can place undue burden on patients and families.

Some opioids may not be appropriate in the end-of-life setting. For example, meperidine is not recommended in cancer pain management due to the neurotoxic effects of its metabolites.[43] In addition, mixed agonist-antagonist opioid analgesics, including butorphanol, nalbuphine, and pentazocine, are not recommended in cancer pain management because they are more likely to cause psychotomimetic effects and they can precipitate the abstinence syndrome if given to a patient who is physically dependent on a pure opioid agonist.[43]

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. Tolerance rarely develops to constipation and therefore it must be prevented and, if unsuccessful, treated aggressively. A prophylactic bowel regimen that includes a laxative and stool softener, such as senna and docusate, should be used, although a recent study suggested that senna alone was just as effective.[44] Bulking agents, such as psyllium, are ineffective and may exacerbate gastrointestinal distress unless the patient can drink significant amounts of fluids. Methylnaltrexone, an opioid antagonist that works on receptors in the GI system and is given subcutaneously, can be used as a rescue when constipation is clearly related to opioid therapy.[45] Two, more recently-approved opioid antagonists are naldemedine and naloxegol.

Sedation is often attributed to opioid therapy given at the end of life, although many other drugs used at this time may be sedating, including benzodiazepines, antiemetics, and other agents. Tolerance to opioid-induced sedation may develop within a few days of regular use; however, in some cases this may persist and opioid rotation may be warranted. A psychostimulant, 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. One study found that with proper timing, the administration of methylphenidate did not disrupt sleep.[46] Other drugs to be considered for similar indications are modafinil (Provigil) and armodafinil (Nuvigil).

Nausea and vomiting are relatively common in opioid-naive individuals. Around-the-clock antiemetic therapy instituted at the beginning of opioid therapy may prevent this adverse effect.[41] The antiemetic can be weaned in most cases after 2 to 3 days. The itching that can occur early in the course of opioid treatment may be at least partially alleviated with antihistamines.

Opioid rotation to a more synthetic agent or an agent with a different route of administration, such as oxymorphone or transdermal fentanyl has also been reported to be helpful.

The potential adverse effect of respiratory depression may lead to clinician under-prescribing of opioids or the reluctance by patients to take the medication.[41] Despite this fear, studies have revealed no correlation between opioid dose, timing of opioid administration, and time of death.[47,48]

Even when a medication, such as an opioid, that is intended to relieve pain and symptoms but does pose a possible risk of hastening death, it is considered ethical for health care providers to prescribe and to administer the medication following the rule of "double effect."[49] This rule distinguishes between practices that are intended to relieve pain but which may have an unintended effect of hastening death vs. practices that are actually intended to hasten death. When an action has both potentially good and bad effects, it is considered ethically acceptable to pursue the action if four conditions are satisfied:[49]

1. The action itself (e.g., administering a pain medication) is not morally wrong.
2. The action is undertaken with the sole intention of bringing about the good effect.
3. The action does not bring about the good effect by means of the bad effect (e.g., in the case of EOL pain medications, such medications do not achieve their effect by ending life).
4. The reason for undertaking the action is clear and urgent.

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Non-steroidal Anti-inflammatory (NSAID) Analgesics and Acetaminophen

NSAIDs or acetaminophen may be useful in the treatment of pain conditions mediated by inflammation, including those caused by cancer, such as bone metastases.[41] NSAIDs typically cause less nausea than opioids, though this is most true with low doses. NSAIDS also do not cause constipation, sedation, or adverse effects on mental functioning. NSAIDs may, therefore, be useful for the control of moderate to severe pain, usually as an adjunct to opioid analgesic therapy.[50] The addition of NSAIDs to an opioid may allow a reduction in the opioid dose, although such combinations must be used with care. Typically, the non-opioid co-analgesic agent, such as acetaminophen or an NSAID, has a ceiling dose above which efficacy will plateau as risk for adverse effects increases. Thus, combining these products, either as separately-administered agents or in combination products, are typically used for patients who are not expected to need substantial dose escalations.[19]

Using a combination product when dose escalation is required risks increasing adverse effects from the non-opioid co-analgesic, even if an increase of the opioid dose is appropriate.

Case Study 4

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

Samuel is a 94-year-old man in the late stages of metastatic prostate cancer. The cancer was initially treated 16 years earlier with a radical prostatectomy and adjuvant radiation therapy, but it has recurred with infiltration to his pelvic bones. He has been under home hospice care for the past month. His pain is being treated with transdermal fentanyl which has reduced the nausea he was experiencing with oral ER/LA oxycodone. Now, however, he says he often feels "fuzzy" and "out of it" to the point that he can't remember conversations he has had with his wife or daughter. On a visit by the hospice nurse, Sam complains about this, saying "I want to be able to say goodbye to people, and thank them, but I just feel like a zombie half the time."

1. **How might Sam's competing desires for pain relief and mental clarity be addressed?**_____

2. **Are there any alternative pharmacological or non-pharmacological analgesic options that might be appropriate for Sam?**_____

3. **What other types of health care professionals might be called on to help Sam achieve the kinds of end-of-life communication he desires?**_____

In such cases, using a pure opioid may be preferable. (Single-agent formulations are available for many types of opioids, such as morphine, oxycodone, and hydromorphone.) The FDA has limited to 325 mg the amount of acetaminophen allowed in prescription opioid combination products in an attempt to limit liver damage and other ill effects primarily due to excessive doses of combined products.[51]

Contraindications for NSAIDs include decreased renal function (relatively common at the end of life) and liver failure. Platelet dysfunction or other potential bleeding disorders, common due to cancer or its treatment, are also contraindications to non-selective NSAIDS because of their inhibitory effects on platelet aggregation, with resultant prolonged bleeding time.[52] Concurrent use of anticoagulants (Coumadin for example) is also a contraindication. Proton pump inhibitors or misoprostol may be considered to prevent GI bleeding.[53]

Attention has recently been focused on the potential limited efficacy of acetaminophen in older patients. Although it has been considered a viable co-analgesic with opioids, and to be first-line therapy in elderly patients with musculoskeletal pains or pain associated with osteoarthritis, the relative limited efficacy and significant adverse effects of this agent, particularly hepatic and renal toxicity, have raised concerns.[54] Reduced doses of 2000 mg/day or the avoidance of acetaminophen is recommended in the face of renal insufficiency or liver failure, and particularly in individuals with a history of significant alcohol use.[55]

Adjuvant Analgesics

Although opioid medications are a mainstay of pain management at the end-of-life, many other classes of medications have proven effective and, in some cases, preferable to opioids (see Table 6). Some exert a direct analgesic effect mediated by non-opioid receptors centrally or peripherally. Other adjuvant "analgesics" have no direct analgesic qualities but may provide pain relief indirectly by affecting organs or body systems involved in painful sensations.

Some antidepressant agents appear to exert analgesic properties and may be particularly helpful for neuropathic pain conditions. Tricyclic antidepressants inhibit reuptake of norepinephrine and serotonin, which appears to exert analgesic effects, either directly or indirectly. These agents have been shown to provide clinically relevant effects in a review of analgesic studies conducted in neuropathic pain conditions, primarily diabetic neuropathy and other non-cancer conditions.[57] Potential side effects include cardiac arrhythmias, conduction abnormalities, narrow-angle glaucoma, and clinically significant prostatic hyperplasia. On the other hand, the sleep-enhancing and mood-elevating effects of these antidepressants may benefit some patients.

Although little evidence supports an analgesic effect for SSRIs, some newer antidepressants, such as the serotonin-norepinephrine reuptake inhibitors have been shown to be effective in relieving neuropathic pain, including venlafaxine and duloxetine.[58] These have the added advantage of alleviating hot flashes, a common and disturbing symptom, particularly in breast cancer patients undergoing hormonal therapy. Care must be taken in such situation, however, because duloxetine reduces the bioavailability of tamoxifen, potentially reducing its therapeutic efficacy.[59]

The anti-epilepsy drugs gabapentin and pregabalin have undergone extensive testing in many non-cancer neuropathy syndromes, and a recent review concluded that these drugs have a clinically meaningful effect.[57]

The most common adverse effects reported by patients are dizziness; some patients also develop fluid retention. Although the data for the efficacy of other anticonvulsants are not as conclusive as those for gabapentin and pregabalin, existing reports suggest potential efficacy. As with most adjuvant analgesics, antiepileptic agents are commonly used in combination with opioid therapy, particularly when pain is moderate to severe. A review of cancer trials found that adjuvant analgesics added to opioids provide additional relief, usually within 4 to 8 days, with the strongest evidence for gabapentin.[60]

Corticosteroids can play a valuable role in treating end-of-life pain related to neuropathic pain syndromes, pain associated with stretching of the liver capsule due to metastases, for treating bone pain (due to their anti-inflammatory effects) as well as for relieving malignant intestinal obstruction.[61] Dexamethasone produces the least amount of mineralocorticoid effect and is available in a variety of delivery forms, including oral, intravenous, subcutaneous, and epidural.[41]

Local anesthetics may be useful in preventing procedural pain and in relieving neuropathic pain. Local anesthetics can be given topically, intravenously, subcutaneously, or intraspinally. Both gel and patch versions of lidocaine have been shown to reduce the pain of postherpetic neuralgia and cancer-related neuropathic pain.[62]

Intravenous or subcutaneous lidocaine at 1 to 5 mg/kg administered over 1 hour, followed by a continuous infusion of 1 to 2 mg/kg/hour, has been reported to reduce intractable neuropathic pain in patients in inpatient palliative care and home hospice settings.[63]

Table 6. Adjuvant Analgesics for End-of-Life Pain Management[56]				
Drug Class	**Agent**	**Route of Administration**	**Potential adverse effects**	**Indications**
Antidepressants	Nortriptyline	Oral	Anticholinergic effects	Neuropathic pain
	Desipramine	Oral	Cardiac arrhythmia	
	Venlafaxine	Oral	Nausea, dizziness	
	Duloxetine	Oral	Nausea	
Anti-epilepsy drugs	Gabapentin	Oral	Dizziness	Neuropathic pain
	Pregabalin	Oral	Dizziness	
	Clonazepam	Oral	Sedation	
Corticosteroids	Dexamethasone	Oral/IV/Sq	"Steroid psychosis"	Neuropathic pain, cerebral edema, spinal cord compression, bone pain, visceral pain
Lidocaine	Lidocaine patch	Topical	Erythema (rare)	Neuropathic pain
	Lidocaine infusion	IV/sq	Perioral numbness, cardiac changes	Intractable neuropathic pain
NMDA antagonists	Ketamine	Oral/IV/intranasal/ topical	Hallucinations	Unrelieved neuropathic pain; need to reduce opioid dose
Bisphosphonates	Pamidronate Clondronate Alendronate Zoledronic acid	IV IV	Pain flare, osteonecrosis	Osteolytic bone pain
Cannabinoids	Dronabinol (Marinol®)	Oral	Dizziness, nausea, tachycardia, euphoria	Pain, nausea, loss of appetite, spasticity
	Nabilone (Cesamet® and Syndros®)	Oral		

NMDA antagonists (dextromethorphan, amantadine, and ketamine) are believed to exert their analgesic effects by blocking receptors for glutamate and other excitatory amino acids at the level of the spinal cord. Ketamine is the most commonly-used agent, and can be administered intravenously, intramuscularly, subcutaneously, intranasally, sublingually, rectally, and topically. A general recommendation is to reduce the opioid dose by approximately 25% to 50% when starting ketamine to avoid sedation.[41] Psychotomimetic reactions consisting of hallucinations, vivid imagery delirium, confusion, and irrational behavior have been reported to occur in approximately 12% of individuals receiving the drug systemically.[42] Adverse effects, including hallucinations and unpleasant cognitive sensations, responded to diazepam at a dose of 1 mg intravenously.[42]

In recent years there has been a resurgence of interest in the use of cannabinoids for the relief of pain and the end of life. Like opioids, cannabinoids produce their pharmacological effects via actions at specific receptors in the body that are designed for endogenously produced compounds with normal regulatory, homeostatic properties.[64] Unlike opioids, however, there has never been a documented case of death from cannabis overdose—indeed, cannabis has no known lethal dose.[65]

The CB1 and CB2 receptors have been shown to mediate the analgesic effects of cannabinoids.[66] This has allowed for the development of more selective agents that may provide analgesia while minimizing cognitive or perceptual side effects. Two oral cannabinoid preparations are FDA-approved and available in the US (dronabinol and nabilone). These routes of administration avoid the potential hazards and dosing uncertainties involved with inhaled or edible forms of cannabis. A review of the existing literature evaluating the role of cannabinoids currently approved for human use suggests that these agents are moderately effective for neuropathic pain with adverse effects that are less than or comparable to existing analgesics.[67]

Cannabinoids have been shown to exert no appreciable effects on opioid plasma levels and may even augment the efficacy of oxycodone and morphine in patients suffering from a variety of chronic pain conditions, potentially allowing a reduction in the opioid doses used in such patients.[68] The authors of a review of the role of cannabinoids in hospice and palliative care concluded: "Many patients in a palliative care setting who are currently on long-term opioids for chronic pain could potentially be treated with either cannabis alone or in combination with a lower dose of opioids. From a pharmacological perspective, cannabinoids are considerably safer than opioids and have broad applicability in palliative care."[64]

Complementary/alternative strategies

A wide range of complementary and alternative therapies (CAT) are commonly used in end-of-life care.[69] More than half of providers that offered CAT offered massage, supportive group therapy, music and pet therapy, guided imagery, and relaxation techniques.[70]

Behaviors likely to respond to CAT interventions include: aggression, disruption, shadowing, depression, and repetitive behaviors (Table 7). Interventions should be matched to the specific needs and capabilities of the patient, and they can be used concurrently with any medications that might be employed.[71,72]

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.[41]

Physical modalities such as massage, use of heat or cold, acupuncture, acupressure, and other physical methods may be provided in consultation with physical or occupational therapy. These treatments can enhance patients' sense of control as well as greatly reduce the family caregivers' sense of helplessness when they are engaged in pain relief. One study found that both massage and "simple touch" induced statistically significant improvements in pain, quality of life, and physical and emotional symptom distress over time without increasing analgesic medication use.[79]

Psychosocial interventions for end-of-life pain may include cancer pain education, hypnosis and imagery based methods, and coping skills training.[80] 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.[80]

Coping skills training may be beneficial for patients and family caregivers dealing with chronic cancer pain, although the dose and components of a coping skills training regimen remain uncertain.

Table 7. Potentially helpful alternative interventions for EOL symptoms[72]	
Intervention	**Applications/indications**
Environmental modifications[73,74]	Support normal sleep/wake cycles Structure activities to reduce boredom Reduce unnecessary stimulation Create home-like environment
Music therapy[75]	Receptive music therapy (listening to music by a therapist who sings or selects recorded music for the recipients). Active music therapy (recipients engage in music-making by playing small instruments, with possible encouragement to improvise with instruments, voice, or dance.) Also music played when doing routine daily care etc.
Bright light therapy[76]	Exposure to simulated or natural lighting to promote circadian rhythm synchronization.
Aromatherapy[77]	Use of plant and herb-based essential oils (indirect inhalation via room diffuser, direct inhalation, aromatherapy massage, or applying essential oils to the skin).
Pet therapy[76,78]	Several small studies suggest that the presence of a dog reduces aggression and agitation, as well as promoting social behavior in people with dementia.

Other integrative and behavioral approaches found to be helpful for managing end-of-life pain are massage therapy and acupuncture.[81]

Managing Pain in Intensive Care Units

Several studies show that most US adults wish to die at home.[82] And yet more than half of deaths occur in hospitals, most with ICU care.[83] When curative approaches are not expected to be successful, a transition to primary comfort-focused care and the withdrawal of ineffective or burdensome therapies is often the compassionate course. Although guidelines and detailed strategies have been developed for analgesic therapy during the removal of life-sustaining interventions, communication about what to expect and how things may proceed remain paramount to negotiating this care transition.[84] Some patients and families may be able to have meaningful interactions at the end of life, and thus brief interruption of sedatives and analgesics may be reasonable.

Rarely are dying ICU patients able to self-report information about their pain.[84] Thus it is incumbent on the critical care health professionals, perhaps with the assistance of the patient's family members, to assess pain without self-report input from the patient. Two pain assessment instruments have been validated for use in the ICU setting: the Behavioral Pain Scale[85] and the Critical-Care Pain Observation Tool.[86] Both tools describe specific observations that the patient's ICU care providers (including family members or loved ones) can make that, when present, could indicate the patient is experiencing pain such as grimacing, rigidity, wincing, shutting of eyes, clenching of fists, verbalization, and moaning.[87]

Reports by family members or other people close to a patient should not be overlooked. In the Study to Understand Prognosis and Preference for Outcomes and Risks of Treatment (SUPPORT) study, surrogates for patients who could not communicate verbally had a 73.5% accuracy rate in estimating presence or absence of the patient's pain.[88]

Managing common EOL symptoms

Effective symptom control can allow patients at the end of their lives to pass through the dying process in a safe, dignified, and comfortable manner. When possible, proactive regimens to prevent symptoms should be used since it is generally easier to prevent symptoms than treat acute symptoms. Because disrupted swallowing function and changes in levels of consciousness can affect patients' ability to swallow pills, medications must be provided in formulations that are safe and feasible for administration. Concentrated sublingual medications, dissolvable tablets, transdermal patches, creams or gels, and rectal suppositories can be used in patients with impaired swallowing or decreased responsiveness.

Nutrition and Hydration

The provision of nutrition and hydration can become a clinical challenge at the end of life and can be directly related to the use of analgesics, particularly in decisions about the preferred route of analgesic administration. As with decisions about analgesia itself, the fundamental question regarding various alternatives for nutrition or hydration is whether the potential benefits outweigh the burdens from the patient's perspective. The patient's own expression of interest should be the primary guide.

If a dying patient shows interest in either food or fluids, they should never be withheld unless providing them clearly causes greater suffering (i.e., in patients for whom oral feeding causes significant discomfort).[39] In most cases, patients either do not show an active interest in food or are satisfied with very small amounts of specific foods (such as sweet custards or ice cream) which are well-tolerated. The forced administration of nutrients, either parenterally or through a nasogastric or gastrostomy tube, has little or no benefit to most patients in the last days or weeks of life, and the placement or continuation of an intravenous line or enteral feeding tube can be burdensome. Enteral feeding tubes used during the terminal phase of illness are often more useful as a means of administering medications than nutrients.

Concerns about adequate hydration are frequently misplaced. Relative dehydration can be beneficial during the terminal phase for the following reasons:[39]

- By decreasing urine output urinary incontinence or difficulties of using a bedpan or commode are reduced
- Reduced gastrointestinal secretions may reduce nausea and vomiting
- In cancer patients, pain may be improved by a reduction in tumor edema
- Reduction in oropharyngeal and pulmonary secretions may lead to reduced airway congestion and diminished pooling of secretions the patient cannot clear on his or her own

Nausea and vomiting

Multiple neurotransmitter pathways in the brain and gastrointestinal tract mediate nausea and vomiting, both of which are common in EOL care. Some therapies for nausea (e.g., haloperidol, risperidone, metoclopramide, and prochlorperazine) target dopaminergic pathways to inhibit receptors in the brain's chemoreceptor trigger zone.[89] Serotonin 5-HT_3 receptor antagonists such as ondansetron and palonosetron have been used to treat chemotherapy and radiation therapy related nausea, although in studies of patients with EOL-related nausea, these agents have not been shown superior to older dopaminergic agents.[36] Anticholinergic medications such as meclizine or transdermal scopolamine can be added if a vestibular component of nausea is present or suspected. Synthetic cannabinoid agents (e.g., dronabinol) and medical marijuana (in states where it is approved for medical use) may be considered as second-line agents for nausea control, although they should be used with caution because they can provoke delirium and dosing of medical marijuana may be imprecise.

Vomiting can occur due to mechanical bowel obstruction, which is common with pelvic and gastrointestinal cancers. Management with an antiemetic (e.g., haloperidol) as well as corticosteroids and analgesics is recommended.[90]

Dyspnea

Dyspnea is common among patients at the end of life and is associated with many diseases or conditions including end-stage pulmonary and cardiac disease, cancers, cerebrovascular disease, and dementia. A number of mechanisms can be involved in dyspnea including pneumonia, airway hyperreactivity, pulmonary edema, pleural effusions, and simple deconditioning. Assessing the severity of dyspnea can be challenging because most dyspnea scales rely on patient self-report, although the Respiratory Distress Observation Scale (eight variables, 0-16 score) is based solely on observers' clinical assessments.[91] Regardless of a patient's measured oxygen saturation, tachypnea, increased difficulty breathing, restlessness, and grunting are clinical signs of dyspnea.

Opioids are first-line agents for treating dyspnea at the end of life.[36] Opioids help reduce the sense of "air hunger" and, when administered at appropriate doses, do not compromise respiratory status or hasten dying.[92]

Opioids should be selected and administered based on patient's comorbidities, previous opioid exposure, and ease of administration (see Table 8 for initial doses). Morphine and oxycodone are available in concentrated forms and sublingual formulations, which allow rapid administration regardless of a patient's level of wakefulness or swallowing ability.

Delirium and agitation

Delirium and agitation are commonly associated with dementia, but may also occur in patients without diagnosed dementia due to physiological or psychological changes at the end of life. Manifestations can include calling out, screaming, verbal and physical aggression, agitation, apathy, hostility, sexual disinhibition, defiance, wandering, intrusiveness, repetitive behavior and/or vocalizations, hoarding, nocturnal restlessness, psychosis (hallucinations or delusions), emotional lability, and paranoid behaviors.[93,94] When a patient presents with delirium or agitation, the first course of action should be to perform a comprehensive assessment of the symptom(s):

- Antecedents: What are the triggers for the behavior(s)?
- Behavior: Which behavior, or behaviors, are targets for intervention?
- Consequences: What are the consequences of the behavior(s) for the patient and others?

Family, caregivers, and nurses are often in the best position to answer these questions. Understanding these factors may reveal simple and effective interventions. Complex, expensive management strategies and interventions may not be required.

A patient's medical condition or a medication the patient is taking may be the primary trigger for delirium or agitation. Although identifying a trigger through patient history and/or physical examination can be challenging if the patient's cognitive impairment is severe, clinicians should persist and include family and caregivers in the process, if possible. Treatment of a reversible medical problem can be much more effective and safe than deploying either non-pharmacologic or pharmacologic interventions. Reversible causes of new-onset behavioral disorders in the elderly include:

- Acute infection (e.g., urinary tract infection, sepsis)
- Delirium (an acute state of confusion which itself can be the result of a new-onset medical condition)
- Depression
- Dehydration
- Hypoxia (e.g., congestive heart failure, pneumonia, anemia due to gastrointestinal hemorrhage)
- Pain (e.g., vertebral or hip fracture, or acute abdominal pain)
- Medication side effect
- Emotional stress
- Reactions to changes in care, caregivers, or caregiver behaviors
- Boredom

Many medications routinely used by older adults can cause or worsen behavioral and psychological problems. For example, anticholinergic agents increase the risk of visual hallucinations, agitation, irritability, delirium, and aggressiveness. Psychotropics, such as benzodiazepines, can impair cognition, be disinhibiting, and may contribute to falls. Adverse drug effects are one of the most common reversible conditions in geriatric medicine. They present an opportunity to effect a cure by stopping the offending drug or lowering the dose. This has led to the recommendation that "any new symptom in an older patient should be considered a possible drug side effect until proven otherwise."[95]

Non-pharmacologic management options for delirium and agitation

Evidence suggests that non-pharmacologic approaches to delirium or agitation can produce equivalent outcomes, in a much shorter time and at less overall risk and cost, than pharmacologic therapies.[96,97] A meta-analysis of community-based non-pharmacologic interventions for delirium or agitation found significant reductions in symptoms as well as improvements in caregiver's reactions to these symptoms.[97] Behaviors more likely to respond to such interventions are: agitation, aggression, disruption, shadowing, depression, and repetitive behaviors. Non-pharmacologic interventions should always be matched to the specific needs and capabilities of the patient, and they can be used concurrently with any pharmacologic therapies that might be employed.[71,72,98]

Behavioral and psychological symptoms often arise in response to a wide range of factors that can make life uncomfortable, frightening, worrisome, irritating, or boring for people with dementia. Paying close attention to such environmental factors, and eliminating or correcting them, should be the first priority for caregivers.[93] This may require patience, diligence, and a willingness to see the world through the eyes and other senses of the person whose behaviors are challenging. Because sensory deficits are common in older adults, and because vision and hearing deficits, in particular, can increase fearfulness, anxiety, and agitation, any patient displaying delirium or agitation should be assessed for these deficits, and, if any are found, they should be corrected promptly with glasses, improved lighting, magnifying devices, hearing aids, or other techniques.

Other environmental factors that can increase agitation include: temperature (too hot or too cold), noise (in or outside the room or dwelling unit), lighting (too much, too little, or quality), unfamiliarity (new people, new furniture, new surroundings), disrupted routines, needing assistance but not knowing how to ask, being uncomfortable from sitting or lying on one position for too long, or inability to communicate easily because of language difficulties.

Dietary and eating-related issues should be carefully assessed. An inability to chew properly or swallow easily can increase agitation, hence a patient's dental integrity, use of false teeth or other orthodontia, and swallowing ability should be considered. If a patient's appetite or cycle of hunger/satiety is not synchronized with the timing of meals provided by an institution, consider options to individualize the availability of food and/or food choice. Difficulty preparing or eating meals, confusion about mealtimes, apathy, agitation, and paranoid ideation about food and fluids may all contribute to weight loss, which is common in patients with dementia. Avoidance of alcohol and caffeine can promote good sleep hygiene and may help stabilize mood.[99]

Pharmacologic management options

Although pharmacologic interventions may be necessary in some circumstances, they should only be considered if the patient is not responding to appropriate, sustained, patient-tailored non-pharmacologic interventions. Two classes of medications should be used very cautiously: benzodiazepines and antipsychotics.

Table 8. Initial opioid doses for dyspnea or pain in opioid-naïve EOL patients[36]

Medication	Oral dose	IV or subcutaneous dose	Initial dosing frequency
Fentanyl	Transmucosal 100-200 mcg	25-100 mcg	Every 2-3 hrs.
Hydromorphone	2-4 mg	0.5-2 mg	Every 3-4 hrs.
Morphine	2.5-10 mg	2-10 mg	Every 3-4 hrs.
Oxycodone	2.5-10 mg	NA	Every 3-4 hrs.

Although benzodiazepines may help treat anxiousness or agitation in the last hours or days of life, use across longer time frames should be avoided in the treatment of delirium or agitation because they may cause or exacerbate a range of problems including:[98,100,101]

- Cognitive impairment
- Rebound insomnia (i.e., if taken as needed, patients sleep worse on the nights that they omit it)
- Risk of falls
- Paradoxical agitation
- Physical dependence with regular use[102]
- Aspiration and its consequences

Antipsychotic medications, while of potential utility in patients with severe or uncontrollable delirium or agitation, should be avoided until other reasonable medications have been tried because of their relatively high risk of side effects and adverse events, including possible death. In June 2008, the US Food and Drug Administration (FDA) determined that both conventional and atypical antipsychotics increase the risk of death in elderly patients, and reiterated that antipsychotics are not indicated for the treatment of dementia-related psychosis.[103]

Initiation of any medication for delirium or agitation should be at the lowest possible dose, with slow titration upwards if needed to the lowest effective dose. Patients must be monitored closely for both adverse effects and drug-drug interactions. If a medication is demonstrated to be effective, the patient should be reassessed frequently, since delirium or agitation symptoms are inherently unstable and subject to remission.

Constipation

Constipation is common at the end of life (because of low oral intake of food and fluids and the adverse effects of opioids) and should be closely managed because it can lead to pain, vomiting, restlessness, and delirium. Prevention generally involves a stimulant laxative (e.g., senna) with a stool softener (e.g., docusate or polyethylene glycol). If constipation does not resolve with these measures, stronger laxatives, suppositories, or enemas are indicated. Methylnaltrexone, naldemedine, and naloxegol can be used to treat opioid-related constipation that does not respond to traditional preventive or treatment regimens.

Caring for a Person Near Death: Tips for Family Caregivers[104]

- Continue to talk to the person and say the things you need or want to say. Remember that the person may be able to hear, even when not able to respond
- Allow the person to sleep as much as he or she wishes
- Reposition the person if it makes him or her more comfortable
- Moisten the person's mouth with a damp cloth
- If the person has a fever or is hot, apply a cool cloth to the forehead
- Give medications as ordered to decrease symptoms such as anxiety, restlessness, agitation or moist breathing
- Keep a light on in the room, it may be comforting
- Play the person's favorite music softly
- Encourage visitors to identify themselves when talking to the person
- Keep things calm in the environment
- Open a window or use a fan in the room if the person is having trouble breathing
- Continue to touch and stay close to your loved one

Ethical Considerations

A potential barrier to good pain management at the end of life is the misconception on the part of providers, family members, or both, that an escalation of pain medications or other palliative therapies will unethically hasten or cause death. Although ethical and legal consensus upholds the appropriateness of withdrawing unwanted or unhelpful therapies to avoid the prolongation of the dying process and the administration of medications with the intent of relieving suffering, such concerns may mitigate optimal administration of therapies.[105] When providers administer pain medications and other palliative therapies to a dying patient, the intent should explicitly be on relief of symptoms, and communication with the family must stress this goal, even if the possibility exists that such treatments could hasten death.[84]

The doctrine of double effect draws a clear distinction between the aggressive palliation of pain with the intent to relieve suffering and the active and purposeful hastening of death. The doctrine asserts that the alleviation of pain is ethically justifiable as long as the caregiver's primary intent is alleviating suffering.[39] (The doctrine of double effect holds that an act that might have a good or bad effect is ethical if the nature of the act is morally good or neutral and the intent of the act is good even if there is potential for bad effect.)[39] Health-care providers should communicate this strategy with patient and families and document the rationale for any dose escalation used for the alleviation of pain.

Contrary to fears among patient and their families, research suggests that aggressive pain management at the end of life does not necessarily shorten life. In fact, pain management may be life-prolonging by decreasing the systemic effects of uncontrolled pain that can compromise vital organ function.[106]

If a patient experiences intense pain, discomfort or other undesirable states at the end of life despite the best efforts of pain management providers, palliative sedation (also known as terminal, continuous, controlled, or deep-sleep sedation) is an option.[84] Palliative sedation is the intentional sedation of a patient suffering uncontrollable refractory symptoms in the last days of life to the point of almost, or complete, unconsciousness and maintaining sedation until death—but not intentionally causing death.[107]

Although palliative sedation may bring intolerable suffering to an end and allow people to die peacefully, it nonetheless can be challenging to put into practice and has been criticized as "slow euthanasia."[93]

Acknowledging the inherently complex and subjective nature of decisions about palliative sedation, guidelines have nonetheless been developed to help guide responsible use of this alternative. Many guidelines state that palliative sedation should only be considered when:[94,108]

- The patient is terminally ill
- Death is expected within hours or days
- The patient is suffering acute symptoms unresponsive to therapy
- Consent is obtained from the patient or his/her proxy
- The withdrawal of food and water is discussed
- Families are informed that the patient will likely not regain consciousness and will die
- Causing death is not the intention even though it may not be possible to achieve adequate symptom control except at the risk of shortening the patient's life

The degree to which palliative sedation is used, and the manner in which it is used, must, in the end, be a matter of clinical judgment on the part of individual physicians.

Palliative/End-of-Life Care Conclusions

Compassionate care for patients who are dying requires clinicians to employ the full range of their therapeutic skills to holistically care for the physical, psychological, and emotional needs of both their patients and loved ones. This is a time when diagnostic skills and medical knowledge may be less important that emotional intelligence and communication skills. It may also entail a shift away from previous goals of aggressive treatment with advanced medical technology, and toward a realistic assessment of what such technology can actually provide in terms of comfort, dignity, and peace of mind at the end of life.

Ongoing pain assessment is critical in order to detect changes in pain such as the development of painful bone metastasis, resolution of treatable causes such as infections, or worsened neuropathic or visceral pain due to tumor growth. Careful refinement of pain management regimens is often required at the end of life and may include changes in the route of analgesics if patients can no longer take oral medications, the need to rotate opioids, or the addition of adjunctive or integrative therapies.

Clinicians should seek expert consultation from pain services or palliative care teams for complex cases or when pain appears to be refractory to all efforts. Early referral to hospice care may allow time for a carefully planned pain regimen to ensure comfort at the end of life. The other symptoms that can accompany the end of life, such as dyspnea, agitation, delirium, and anxiety, each need to be carefully assessed and treated with coordinated interventions.

Fortunately, a wide array of analgesics, interventional strategies, adjuvant medications, varied routes of administration, and complementary and alternative therapies exist that, if used cooperatively and effectively, can greatly improve the chances that patients and their families will experience death without trauma, suffering, or unrelieved pain.

Introduction to Pain Management

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience arising from actual or potential tissue damage or described in terms of such damage."[110] Pain can be characterized as either acute or chronic pain. Acute pain typically has a sudden onset and a specific cause and is often described as sharp pain. Acute pain typically lasts for a short period, less than three months, and goes away when there is no longer an underlying cause for the pain.[111,112]

Chronic pain is ongoing and typically lasts longer than three to six months, or past the amount of time needed for normal tissue healing.[113] Common causes of chronic pain include lower back pain, nerve pain, arthritis, and fibromyalgia. Chronic pain can affect many aspects of a patient's life, causing adverse effects that include depression, fatigue, worsened comorbid conditions, and negative effects on social relationships.[114]

Pain disorders, exclusive of cancer or end-of-life pain, are often referred to collectively as chronic noncancer pain (CNCP). Chronic pain is one of the most common reasons that adults seek medical care in the United States, and is associated with poor mental health, decreased quality of life, and opioid dependence. The 2019 National Health Interview Survey found that in the previous three months, 20.4% of adults experienced chronic pain, and 7.4% had chronic pain that limited their work or life activities, known as high-impact chronic pain. The incidence of both chronic pain and high-impact chronic pain increased with age, with the highest prevalence in people over the age of 65. Incidence was also higher in rural areas, and among women as compared to men.[115]

Pain is a highly subjective and personal experience that can be effectively described only by the person who is experiencing pain. Recognizing and accepting the subjectivity of pain are significant challenges of treating pain that must be overcome to provide appropriate care.[110]

Evaluation of the Pain Patient

It is critical to fully characterize both the patient's pain condition and their potential for misusing or abusing controlled substances. Specifically, healthcare professionals must complete a comprehensive physical, medical, and social history and include an assessment of substance abuse and consideration of any special population requirements. Diligent healthcare professionals will look beyond the specific complaint and holistically evaluate the broader mental, cultural, and socioeconomic contexts in which the chief complaint is embedded.[116]

A comprehensive history should be taken before a physical examination. A good medical history assessment is a test of the provider's knowledge and communication skills. Depending on the mental state and reliability of the patient, a collateral history from a friend, relative, or caregiver may be required. It may be possible to gather this information before an in-person visit by using paper or online questionnaires. The history should include the following:[117]

- Past medical and surgical history to determine the etiology of pain and comorbidities that may affect therapy.
- A review of systems to evaluate the effects of pain.
- Social and family history, which helps elicit any issues pertaining to the development and treatment of pain.
- Reviewing psychiatric comorbidities, which may require co-treatment.
- Assessment of pain, including history, location, characteristics, severity, and impact.

It is critical to gain as much information as possible about the specific complaint of pain. The *SOCRATES* acronym is a useful tool to remember key points to be collected when assessing a complaint of pain:[116]

- **S**ite: Where exactly is the pain?
- **O**nset: When did it start? Was it constant or intermittent? Was it gradual or sudden?
- **C**haracter: What is the pain like? Sharp? Burning? Tight?
- **R**adiation: Does the pain radiate or travel anywhere?
- **A**ssociations: Are there any symptoms associated with the pain such as sweating or vomiting?
- **T**ime course: Does it follow any time pattern? How long does it last?
- **E**xacerbating and relieving factors: Does anything make it better or worse?
- **S**everity: How severe is the pain? Consider using a visual analog scale or numeric rating scale to characterize the level of pain experienced by the patient. These scales allow patients to rate their pain between 0 (no pain) and 10 (worst pain imaginable).

Psychosocial Evaluation

Pain affects every aspect of a patient's life. Therefore, it is vital to evaluate the ways pain may be affecting, or may be affected by, a patient's mental health. Clinicians must be alert for signs of depression or anxiety, which are very common in patients suffering from chronic pain. Be particularly alert for suicidal thoughts; the risk of suicide is roughly doubled for patients with chronic pain.[118,119]

Referral to a mental health professional is warranted if the clinician's judgment suggests that the patient has active psychological issues beyond their expertise. Clinicians should also probe for ways in which pain may be affecting the patient's family system, work, or social activities. Pain can seriously erode these spheres of life. Evaluating these challenges and addressing them during treatment (for instance, by referral to a vocational counselor or social worker) is just as important as treating the more immediate medical issues that may be contributing to chronic pain.[118,119]

Treatment Plans

A comprehensive written plan should be developed to help both patients and providers work toward the patient's pain management goals. Since the use of pain ratings alone to determine treatment goals can be problematic, one realistic approach may be to employ a function-based strategy. Using this method, the clinician does not measure efficacy as a patient's progress in achieving pain relief, but rather by their ability to objectively achieve improved function. Potential post-therapeutic goals could include the ability to go to work, walk, enhanced sleeping, or simply improved social interactions. Possible functional scales could include one or two activities with minimal impact – for example, work enjoyment or pain-free walking – with intermediate steps interspersed.[120]

Function-based goals offer two key advantages for managing medication use in patients with chronic pain[120,121]:

- Prescribing decisions are based on outcomes that can be objectively demonstrated to both the provider and the patient or caregiver.
- Individual differences in tolerance to pain become secondary to setting and monitoring treatment goals, since the patient's perceived pain levels are not the focus in determining functionality.

If a function-based approach is used, progress can be documented independently of subjective swings in reported pain. It is critical that the patient understands that progress may not be measured in days. Rather, gains may be incremental and occur over months or years. Further, some patients who begin showing solid progress may plateau. In these cases, consider reassessment. It may be beneficial to begin with more easily achievable goals to be replaced with more difficult goals after initial successes. This approach can be much more motivating than a plan resulting in early treatment failure.[120,121]

As with most patient-provider documents, patients should be reminded of the potential risks and benefits of therapy even after obtaining informed consent. The realities of tolerance and physical dependence to controlled substances cannot be over-emphasized. Another key component is a description of how treatment might be terminated. It is critical to discuss the conditions that could lead to the discontinuation of therapy. Opioids are not curative and have no standard duration of treatment. Termination may become necessary for many reasons, including:[118,122]

- Healing or resolution of the cause of pain.
- Experiencing significant side effects.
- An inadequate response to medication in terms of either pain relief or functional improvement.
- Evidence of nonmedical or inappropriate use of the medication.

If inappropriate use of a prescription medication leads to termination, referral to a provider with specialized skills or experience in dealing with high-risk patients may be prudent.[118,122]

Non-Pharmacological Pain Management

When evaluating the options available to a particular patient for the treatment of pain, providers should maximize the use of nonpharmacologic therapies. Nonpharmacologic therapies can be grouped into several categories: exercise therapy, psychoeducational interventions, mind-body therapies, and physical interventions such as chiropractic manipulation, acupuncture, and massage. Combining therapies may be more effective for maintaining long-term relief than any single treatment. The choice of therapy is based on a number of patient-specific factors, such as the type of pain, preference, cost, access, and patient values.[123] Maximizing the use of nonpharmacologic treatment options, and combining their use when appropriate, can improve pain control and reduce the reliance on opioids.[118]

Useful in both acute and chronic musculoskeletal pain conditions, physical therapy helps patients work towards the goal of improved physical function. It involves working with a physical therapist to develop patient-specific exercises that allow patients to feel safe while being physically active, encouraging patients to increase daily activity levels. Physical therapy can also address deconditioning and fear-avoidance seen in chronic pain patients. It has been shown to demonstrate moderate effects on disability and pain while improving quality of life, anxiety, and depression.[123]

Therapeutic exercise is low-impact exercise programs, such as aquatic exercise, yoga, or tai chi. Studies show that exercise therapy for chronic pain can reduce pain and improve function with few adverse effects. The American College of Physicians recommends structured exercise, yoga, and tai chi among their other first-line therapies for chronic pain.[123]

Psychological therapies are recommended for patients who have pain that impacts their mood, quality of life, sleep, or relationships with others. The most commonly recommended and best-studied psychological therapy for chronic pain is cognitive-behavioral therapy. It addresses the way that a patient's thoughts interact with their actions, targeting maladaptive behavioral and cognitive responses to pain. Patients are taught to increase awareness of thoughts in order to reduce the severity of painful symptoms using a range of strategies to modify their interactions with their environment.[123]

Mind-body therapies describe a broad range of treatments that address a patient's thoughts, emotions, movement, behaviors, and body awareness. It includes mindfulness-based stress reduction, deep breathing, relaxation, and meditation. Evidence supporting mind-body therapies is of poor quality, often due to the difficulty in studying these therapies, but suggests some benefit. A 2020 meta-analysis found the use of mind-body therapies lead to moderate improvements in pain and small reductions in opioid dose in both acute and chronic pain patients treated with opioids.[123]

Acupuncture, originating from traditional Chinese medicine, is one of the oldest healing practices in the world. Acupuncture stimulates specific points in the body, usually by inserting thin needles through the skin. According to the traditional Chinese medicine theory, this regulates the flow of vital energy (called qi) along pathways called meridians. It is recommended by the American College of Physicians to include acupuncture among the first-line non-pharmacological treatments for chronic low back pain. It may be appropriate to consider acupuncture in some cases of pain management.[124]

Chiropractic manipulation is a form of manual therapy that involves correcting the alignment of a joint. A meta-analysis of over 6000 patients across 26 trials found that spinal manipulation in patients with chronic low back pain resulted in small short-term reductions in pain, as well as improved functional status when compared with a variety of other interventions including medications and physical therapy.[125] Massage can also be used in the treatment of pain, and while there is limited evidence to support its use, the harms from massage appear to be minimal, and some patients report symptomatic relief, making it a reasonable adjunctive treatment.[126]

Pharmacologic Treatment of Pain: Non-Opioid Medications

Just like the causes of pain, available treatments are also diverse. Pharmacologic treatment options run the gamut from over-the-counter pain relievers to controlled substances, with many alternatives in between. Because of the many different pathologies, it is critical that if one approach fails, another is tried. When it comes to pain management, no single treatment is guaranteed to work as intended. Further, relief may be found using a combination treatment approach. Milder pain episodes can often be treated using over-the-counter medications including acetaminophen and non-steroidal anti-inflammatory agents (NSAIDs).[118,127]

Acetaminophen

Acetaminophen is a common choice for treating fevers as well as easing pain. Its mechanism of action in analgesia is unclear, but it is thought to reduce the synthesis of prostaglandins in the central nervous system. Acetaminophen does not exhibit anti-inflammatory effects in the peripheral nervous system and is typically reserved for pain without inflammation. Even though it is commonly used, there is only limited evidence of its efficacy in treating chronic pain. However, it is known to provide analgesic effects for some patients, and it is reasonable to consider using acetaminophen as an adjunct for mild to moderate musculoskeletal pain.[128,129]

Typical doses of acetaminophen are 325-650mg every 4 to 6 hours, or 1000mg up to three times daily. Acetaminophen is associated with hepatotoxicity when taken in high doses, particularly in cases of acute or chronic overdose; therefore, the maximum daily dose should be limited. There is some debate over the maximum daily dose of acetaminophen. The Food and Drug Administration recommends a maximum dose of 4 grams per day. However, when used long term, many experts recommend a maximum of 3000mg per day, and even lowering this to 2000mg per day in older patients, patients who have or are at risk of liver disease such as those with alcohol use disorder or malnourishment, and patients with organ dysfunction.[129,130]

While acetaminophen does not appear to interact with platelet function or increase the risk of bleeding, it is known to interact with warfarin and may require more frequent INR monitoring. It also interacts with isoniazid and other agents that induce the CYP450 enzyme system.[130]

Acetaminophen is found in a number of prescription and over-the-counter products. Patients should be counseled to be aware of the acetaminophen content of other products they are taking and to avoid exceeding their daily limit.[130]

Nonselective Non-steroidal anti-inflammatory agents (NSAIDs)

Nonselective non-steroidal anti-inflammatory agents (NSAIDs) decrease pain and inflammation by blocking cyclooxygenase (COX), thereby decreasing the production of prostaglandins. There are two isoforms of cyclooxygenase, COX-1 and COX-2. COX-2 is upregulated in inflammatory states and is involved in the production of prostaglandins; COX-1 is found in most tissues and regulates normal cellular processes such as gastric protection, platelet aggregation, kidney function, and vascular homeostasis. Nonselective NSAIDs block both COX-1 and COX-2, leading to anti-inflammatory effects as well as adverse reactions.[111,131]

NSAIDs are a mainstay of treatment in musculoskeletal pain with an inflammatory component, such as menstrual cramps or muscle sprains. More than 17 million Americans use NSAIDs on a daily basis, making them one of the most commonly used classes of medications in the world.[130] However, the efficacy of these medications in pain without ongoing inflammation, such as low back pain, is low.[111,129]

Examples of nonselective NSAIDs and their typical dosages used for analgesia include:[111]

- Naproxen, 250-550mg every 12 hours
- Ibuprofen, 400mg every 4 to 6 hours
- Ketoprofen, 50mg every 6 hours or 75mg every 8 hours
- Flurbiprofen, 50 to 100mg every 6 to 12 hours
- Oxaprozin, 1200mg once daily
- Diclofenac, 50mg every 8 hours
- Etodolac, immediate release 200 to 400mg every 6 to 8 hours, or extended-release 400 to 1000mg daily

- Indomethacin, immediate release 25 to 50mg every 8 to 12 hours, or controlled release 75mg once or twice daily
- Sulindac, 150 to 200mg every 12 hours
- Meloxicam, 7.5 to 15mg once daily
- Piroxicam, 10 to 20mg once daily

A variety of side effects are associated with NSAIDs; the risk of developing side effects is increased with high, frequent dosing or longer durations. Gastrointestinal effects, such as dyspepsia, peptic ulcer disease, and bleeding, are more likely in patients over 60, those with a prior history of a gastrointestinal event, those taking high doses of NSAIDs, or those taking glucocorticoids, antiplatelet drugs, or anticoagulants. Gastrointestinal effects may be reduced by taking the drug with food, milk, or antacids. Adverse effects on the kidneys can include worsening of underlying hypertension, electrolyte and fluid abnormalities, and an increased risk of acute renal failure and renal cell cancer. Patients with existing glomerular disease, hypercalcemia, renal insufficiency, or volume depletion conditions are at an increased risk of developing acute renal failure.[111,130]

Both chronic and short-term use of NSAIDs is associated with an increased risk of myocardial infarction or stroke. In addition, NSAIDs can exacerbate heart failure through sodium and water retention and increases in blood pressure. This risk can be minimized by using the lowest effective dose for the shortest duration possible. Hepatic enzymes can be elevated by NSAIDs, but liver failure is rare. Other rare side effects include anaphylaxis, pulmonary effects such as bronchospasm or pulmonary infiltrates, neutropenia, tinnitus, and life-threatening rashes such as Stevens-Johnson syndrome.[111,130]

NSAIDs have antiplatelet effects that can be beneficial in some patients, such as using aspirin for cardiac prophylaxis in patients with coronary heart disease. However, these effects can create issues in patients with preexisting platelet deficits or when considering surgery. For most NSAIDs, platelet function normalizes within 3 days of discontinuation, suggesting that NSAIDs should generally be discontinued at least 3 days prior to surgery. The antiplatelet effects of NSAIDs can be exacerbated when combined with other antiplatelet agents or anticoagulants, increasing the risk of bleeding. Therefore, NSAIDs should be avoided if possible in patients taking blood thinning agents. Certain antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) also appear to have antiplatelet effects, so combination with NSAIDs can increase the risk of gastrointestinal bleeding.[111,130]

Oral NSAIDs should be avoided in patients with GI bleeding, platelet dysfunction, uncontrolled hypertension, hyponatremia, cirrhosis, and creatinine clearance of less than 60mL/min. NSAIDs should be used cautiously in older adults, due to the increased risk of adverse effects. Lower doses and limited durations are preferable to mitigate these risks.

Topical NSAIDs, such as diclofenac gel or patches, can be considered in these patients to reduce the risk of adverse reactions.[111,130]

Pregnant patients should avoid NSAIDs if possible in order to avoid the risk of adverse pregnancy outcomes. There is limited information on the use of NSAIDs in lactation, but ibuprofen appears to be the preferred agent in these patients since it is only excreted into the breast milk in very small amounts and has the most information available on its safety.[111,132]

Selective COX-2 Inhibitors

A focus of drug development in the early 1990s was to create a product that selectively inhibits COX-2, targeting prostaglandin production without affecting the various cellular processes that rely on COX-1. This led to the development of several products, most of which have been removed from the market due to an increased risk of adverse cardiovascular events. There is one product that remains available in the US — celecoxib.[131] It is typically given in doses of 200mg daily or 100mg every 12 hours.[111,130]

Celecoxib has similar efficacy to NSAIDs in terms of analgesia and anti-inflammatory effects. It is associated with a reduction in gastric toxicity compared to NSAIDs, and little to no effects on inhibiting platelet function, allowing for increased use in patients with bleeding disorders and those at risk for gastrointestinal bleeding. However, like NSAIDs, celecoxib is associated with an increased risk of adverse cardiovascular events, including stroke, myocardial infarction, heart failure, and death. This increased risk is seen in patients with and without pre-existing cardiovascular disease. This risk can be minimized by using the lowest effective dose for the shortest duration possible. In addition, celecoxib can cause acute renal failure, though it appears to be associated with 40% fewer renal events when compared with ibuprofen. The risk of acute kidney injury is increased in patients with chronic kidney disease, those who are volume-depleted due to as aggressive diuresis or heart failure, and those with severe hypercalcemia.[111,131]

Antiepileptic Medications

Gabapentin and pregabalin are anticonvulsants that are approved by the FDA for the treatment of neuropathic pain. Gabapentin and pregabalin both work by binding to the voltage-gated calcium channels in the central nervous system; their true mechanism in pain control is not clear and likely multifactorial. Gabapentin was primarily studied for the treatment of postherpetic neuralgia and diabetic neuropathy; evidence of efficacy in other types of neuropathic pain is limited. When used for neuropathic pain, it is typically initiated at a dose of 300mg at night; older adults and those who are sensitive to sedation should consider starting at 100mg. The daily dose range of 1200 to 2400mg per day is typically most effective for neuropathy, with doses divided into three daily doses. An adequate trial of gabapentin can take two months or longer. Patients with renal impairment require dosage adjustment.[111,129]

A systematic review in 2019 found that among 45 randomized trials, pregabalin was found to be more effective than placebo in treating diabetic neuropathy, postherpetic neuralgia, and mixed neuropathic pain; daily doses of 300 to 600mg were most effective. Pregabalin is also the only medication FDA approved for the treatment of neuropathic pain associated with spinal cord injury. It is recommended to initiate pregabalin at a daily dose of 150mg per day, divided into two to three daily doses. It can be increased to 300 to 600mg per day over the course of two to four weeks if needed. Patients with renal impairment require dosage adjustment. Pregabalin may provide more rapid analgesia than gabapentin, due to the use of lower doses and shorter titration schedules.[111,129]

The most common side effects associated with gabapentin and pregabalin are dizziness and sedation, which are dose-dependent. These effects can be reduced with lower starting doses and slow titration. In addition, respiratory depression has been reported in older adults and patients who received gabapentin along with opioids or other sedatives. One study reported that co-prescribing pregabalin with opioids was associated with a dose-related increase in the risk of opioid-related mortality; similar results have been reported when combining gabapentin with opioids. There are also increasing reports of abuse potential with gabapentin and pregabalin; they should be used with caution in patients with substance use disorders.[111,129]

Muscle Relaxants

Muscle relaxants describe a diverse category of medications with similar effects of analgesia and skeletal muscle relaxation or muscle spasm relief. Muscle relaxants have been shown to provide short-term pain relief in patients with low back pain when compared with a placebo, though their utility in long-term pain treatment is unclear.[134] However, some patients may benefit from the addition of a muscle relaxant, such as those with low back pain who have pain disrupting their sleep and may benefit from their sedating effects, and those at risk of opioid misuse.[111,133]

Skeletal muscle relaxants are recommended as second-line therapy in patients with low back pain whose symptoms are not managed with acetaminophen or NSAIDs alone. If used, cyclobenzaprine and tizanidine are preferred agents because they have more data available to support their use and they have less abuse potential than other agents such as carisoprodol. The lowest effective dose and frequency should be utilized, and these medications are often given on an 'as needed' basis.

Muscle relaxants include agents such as:[111,133,134]

- Cyclobenzaprine 5 to 10mg three times daily as needed, with one dose at bedtime to help with sleep
- Carisoprodol 250 to 350mg three times daily for a maximum of 2 to 3 weeks

- Methocarbamol 750 to 1500mg three times daily
- Metaxalone 800mg 3 to 4 times daily
- Tizanidine 4 to 8mg three times daily as needed

Use of muscle relaxants is associated with significant adverse events, including drowsiness and dizziness. Sedation can be significant, and can limit the patient's ability to drive or work; these effects are more likely in older patients and those with organ dysfunction. Combination with other sedating agents such as opioids and benzodiazepines can exacerbate sedation. It may be best to avoid the use of muscle relaxants in patients with substance use disorders, particularly those who are also utilizing opioids, due to the significant risk of misuse. Use of muscle relaxants should be limited to adjunctive therapy for short-term treatment of acute musculoskeletal conditions.[111,134]

Benzodiazepines

Benzodiazepines are Schedule IV controlled substances that work by potentiating the inhibitory activity of GABA and increasing its ability to exert calming effects. This effect can be helpful in the treatment of anxiety, but can also be addictive[135]. Benzodiazepines are also effective in treating muscle spasms, though their high abuse potential and availability of alternative agents for this purpose make them a non-preferred agent for the treatment of chronic pain.[111,129]

The most commonly reported side effects associated with benzodiazepines are related to central nervous system depression: drowsiness, amnesia, psychomotor impairment, and confusion. Drowsiness is more commonly experienced during the first few days of treatment though tolerance can develop to this side effect. Rebound anxiety can occur after short-term treatment; higher doses can result in withdrawal symptoms and learning impairment. Benzodiazepines with shorter half-lives, such as alprazolam and lorazepam are more likely to cause acute withdrawal when abruptly stopping treatment after prolonged use. Those with longer half-lives, such as diazepam, typically produce more delayed and attenuated withdrawal symptoms.[111,135]

Benzodiazepines must be tapered very slowly when discontinuing after long-term use. A reduction of around 10% per 1-2 weeks is preferred if circumstances allow. Patients should be monitored for symptoms of withdrawal such as anxiety, dysphoria, tremor, perceptual disturbances, psychosis, or even seizures. If withdrawal symptoms develop, the rate of dose reduction should be slowed accordingly.[111,135]

Drug interactions must also be considered when prescribing benzodiazepines. Because they exert depressant effects on the central nervous system (CNS), administration of additional CNS depressants such as opiates, muscle relaxers, sleep medications, and alcohol should be minimized because of the risk of respiratory depression and death.[111]

The U.S. Food and Drug Administration added a black box warning to the labels of all opioids and benzodiazepines advising against using these medications together. Because both are CNS depressants, the combination puts patients at increased risk of slowed or difficult breathing, oversedation, respiratory depression, and death. The CDC recommends that these medications should be prescribed together only when alternative treatments are inadequate. When co-prescribed, the dosages and durations should be kept to the minimum possible.[118]

Benzodiazepines must be used especially cautiously in the elderly. Elderly patients are more susceptible to drug accumulation because of hepatic insufficiency, decreased oxidation, and altered volume of distribution. They are also more sensitive to the central nervous system effects of benzodiazepines regardless of the half-life of the agent used. This results in an increased frequency of falls and associated fractures.[111]

Benzodiazepines should be avoided in pregnant patients. Teratogenic effects such as cleft lip and cleft palate have been associated with benzodiazepine use, particularly during the first trimester, when fetal development is rapid. Benzodiazepine use during the third trimester has been associated with neonatal withdrawal, sedation, and hypothermia in the infant.[111]

Antidepressants

Antidepressants are an important modality in the treatment of many painful conditions. Antidepressants seem to work best for treating neuropathic types of pain, such as neuropathy, nerve damage (post-herpetic neuralgia), migraine, and fibromyalgia. They may also be helpful adjuvants in lower back pain, arthritis, and pelvic pain. The mechanism by which these drugs address pain is not clearly understood, but it is thought that inhibiting norepinephrine reuptake leads to the up-regulation of inhibitory pain pathways. Antidepressants take two to four weeks to exhibit analgesic effects, so some patience is required.[111,129]

The evidence is most supportive of the use of tricyclic antidepressants (TCAs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) for the treatment of pain. Studies have shown that only 3.6 to 6.4 patients with neuropathic pain need to be treated for one patient to achieve at least a 50% reduction in pain relief. TCAs and SNRIs are indicated for the treatment of pain even in the absence of mood disorders, since analgesic effects are known to occur in patients who are not depressed. However, their use in patients with comorbidities of depression and pain can provide significant benefits in the treatment of both disease states.[111,129]

Among the SNRIs, duloxetine and venlafaxine have the most evidence for use in neuropathic pain, and duloxetine also has evidence of efficacy in musculoskeletal pain. Duloxetine is FDA approved for the treatment of fibromyalgia, chronic low back pain, osteoarthritis and diabetic neuropathy. It is typically used in doses of 30 to 120mg daily, with lower doses preferred in patients who are concerned about side effects. Duloxetine should be avoided in patients with hepatic or severe renal insufficiency. Venlafaxine is used in doses of 75-225mg daily for the treatment of acute and chronic neuropathic pain.[111,129]

SNRIs are contraindicated in patients taking MAOIs within the previous two weeks due to the risk of serotonin syndrome, and in some cases, hypertensive crisis. Duloxetine has moderately potent inhibitory effects on the hepatic cytochrome P450 enzyme CYP2D6, resulting in drug interactions with other medications that affect or are affected by this enzyme. Side effects associated with SNRIs include[136]:

- Nausea, which appears to diminish over time
- Dizziness
- Diaphoresis
- Increased blood pressure, due to the effects on norepinephrine
- Headaches
- Sexual dysfunction
- Increased risk of bleeding
- Hyponatremia

While tricyclic antidepressants do not carry FDA approval for pain management, they are used frequently for a number of chronic pain states. Amitriptyline is the most widely studied TCA in chronic pain and is the only TCA with proven efficacy in migraine prevention. When used for pain, amitriptyline can be started at 25mg at bedtime, and slowly increased at weekly intervals up to 125mg daily. Nortriptyline is also used for chronic pain and may be preferred due to its reduced anticholinergic and sedative effects when compared to amitriptyline. Nortriptyline can be started at 10mg daily at bedtime and increased weekly in 10 to 25mg intervals up to 75 to 150mg daily. TCAs should be started at low doses, and doses should only be increased slowly as needed. Low starting doses are particularly important when using TCAs in older adults, who are at a higher risk of being negatively affected by side effects.[129]

Since TCAs are sedating, administration with barbiturates, alcohol or other agents with CNS depressant effects can cause oversedation, impaired functioning, and falls. Medications that increase serotonin levels, including herbal preparations such as St. John's wort and SAM-e, can lead to serotonin syndrome when co-administered. Agents that cause QT prolongation, such as certain broad-spectrum antibiotics, should be used with caution with cyclic antidepressants, due to additive risk. Other agents that lower the seizure threshold, such as tramadol, can increase the risk of seizures when administered with cyclic antidepressants. Side effects associated with cyclic antidepressants include[137]:

- Overdose: as little as 10 times the daily dose of cyclic antidepressants can be fatal, due to QT prolongation causing fatal arrhythmias
- Cardiac side effects, such as orthostatic hypotension, QT prolongation, tachycardia and arrhythmias
- Lower seizure threshold

- Bone fractures
- Anticholinergic effects due to muscarinic receptor blockage, including dry mouth, blurred vision, constipation, urinary retention, confusion, and delirium
- Antihistaminic effects due to histamine receptor blockage, including sedation, increased appetite causing weight gain, confusion and delirium
- Sexual dysfunction
- Diaphoresis
- Tremor

Topical Lidocaine

Data supporting the use of topical lidocaine is limited, though it is used frequently in the treatment of chronic pain. It is considered an adjuvant agent in the treatment of neuropathic pain, with the best evidence supporting its use in postherpetic neuralgia and diabetic neuropathy.[129]

Lidocaine 5% patches are commonly used; a single patch contains 700mg of lidocaine. Up to three patches can be applied at a time for up to 12 hours in a 24-hour period; a 12-hour patch-free period is required each day due to the risk of lidocaine toxicity. Systemic absorption with lidocaine patches is low, averaging 3%, but this requires cautious use in patients with renal, hepatic, or cardiac dysfunction.[129]

Pharmacologic Treatment of Pain: Opioids

Historically, prescribers limited the use of opioids solely to patients with acute or cancer-related pain. Over time, the use of opioids to treat many types of pain has increased to dangerously high levels. Prescription rates of opioids had been steadily rising since the advent of new opioid products in the 1990s, and prescription rates peaked in 2012 with more than 255 million prescriptions for opioids written that year. Opioid prescribing rates have been slowly declining since 2012, with approximately 142 million opioid prescriptions written in 2020.[138]

Declines in opioid prescribing are likely attributed to regulatory restrictions, more stringent clinical practice guidelines, education, and reimbursement controls. However, the opioid epidemic is a major public health crisis that is affecting Americans at alarming rates.[29] According to a report from the Substance Abuse and Mental Health Services Administration (SAMHSA), approximately 9.5 million people misused opioids in 2020. Of those users, 9.3 million participated in the recreational use of prescription painkillers.[139] An estimated 70,000 Americans died from opioid overdose in 2019.[138]

Patient-provider agreements

Agreements between the patient and provider define the roles and responsibilities of the provider and patient when starting opioid therapy. They are used as a means to educate the patient on best practices for opioid use and can serve as a tool to identify concerns as the patient continues utilizing opioid therapy.

Components of an effective patient-provider agreement include[140]:

- The provider and patient's roles and responsibilities are clearly defined
- Requirements that the patient will use one physician for prescribing and one pharmacy to fill prescriptions
- Requirements for the use of both opioid and non-opioid pain medications
- The patient's consent to discuss care with other providers found in the state's Prescription Drug Monitoring Program
- An agreement that the patient will take their medication as prescribed and that refills will not be provided early
- Definitions of the patient's responsibilities in terms of keeping their medication safe and maintaining their supply
- Appointment and drug screening requirements
- Requirements for reporting side effects to the provider
- A plan for what will happen if the benefits of therapy no longer outweigh the risks
- Potential situations where opioids need to be tapered or discontinued for patient safety
- Naloxone training for family and caregivers
- A plan for referral to a specialized provider for opioid use disorder if the patient breaks the agreement or the provider has concerns about the patient developing substance use issues

To be effective, the specifics of treatment must be characterized and explained using a tailored approach for the individual patient and their family or caregiver. This may require agreements to be provided in multiple languages. Agreements should be written at the sixth- to seventh-grade education level, or lower. Translators may be required 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. It is critical to ensure that none of the language used could be interpreted as coercive.[140,141]

Patient-provider agreements are widely used, and come highly recommended for long-term opioid therapy, but their effects on preventing opioid misuse are not clear. A 2021 study found that although 66% of providers thought patient-provider agreements were worth the effort, only 28% considered them effective in decreasing opioid misuse. Despite their minimal effectiveness, providers still perceive these agreements as a valuable tool to use when prescribing opioids.[141]

Informed consent

The choice to start therapy with controlled substances should be a shared decision between the patient and the prescriber.

A discussion of benefits and risks should take place and documenting this discussion through written informed consent paperwork helps to ensure all aspects of the patient's therapy are adequately addressed. Informed consent is a fundamental part of planning for any treatment, but it is critically important in long-term opioid therapy, given the potential risks of such therapy. Informed consent also fosters an open dialogue between the provider and patient, and may help protect the provider and clinic from any legal disagreements.[142]

The Indian Health Service recommends that informed consent documents for opiate therapy should typically address the following concerns[142]:

- The possible risks and benefits of opiate therapy.
- Possible short-term and long-term side effects of opiate therapy such as cognitive impairment, constipation, overdose, and death.
- The risk of developing tolerance and physical dependence.
- The risk of oversedation and drug interactions, including drug-disease interactions such as the higher risk of using opiates in patients with sleep apnea or obesity.
- The risk of impairing motor skills that can affect driving and other tasks.
- The risk of misuse, dependence, opioid use disorder, and overdose.
- The fact that there is little evidence of the benefits of long-term opiate use.
- An agreement for the release of information to coordinate care with other treating providers.

Pharmacology of Opioids

Opioid receptors are found throughout the body, such as in the gastrointestinal tract, pituitary gland, skin, and immune cells, where they carry out various analgesic and non-analgesic functions. Opioids are classified by their effects at the opioid receptors, where they can be agonists, antagonists, partial agonists, or even a combination. An agonist such as morphine activates the receptor, whereas an antagonist such as naloxone blocks the receptor, resulting in no response and preventing agonists from binding to that receptor. Partial agonists such as buprenorphine and tramadol bind to receptors and can provide similar effects to full agonists at low dosages, but when the dosage increases, analgesic activity plateaus, so increased dosages do not increase analgesia but can increase side effects. In addition, some opioids, such as nalbuphine and butorphanol, demonstrate mixed activity that varies based on which opioid receptor is involved and also depending on the dose.[118,143,144]

Each individual's opioid-receptor makeup is unique, which results in significant variability in analgesia, side effects, and tolerance. Additionally, different opioid formulations and analogs have varying properties that affect absorption and pharmacokinetics. For example, fentanyl and its analogs are highly lipophilic, meaning they are fat-soluble. As a result, the onset of action is faster than less lipophilic drugs like morphine.[118,143,144]

Opioid Agonists

Opioid agonists are drugs that bind tightly to opioid receptors to illicit a response. Opioid agonists can be classified further as naturally occurring, semi-synthetic, or synthetic. Commonly prescribed opioid agonists are discussed below.[143]

Morphine

Morphine is the prototype naturally-occurring opioid by which all other opioids are compared. It is available in immediate-release oral formulations, extended-release oral tablets, as well as parenteral formulations. The effects of morphine are primarily due to the parent drug, but its hepatic metabolism creates two metabolites that contribute to its efficacy as well as toxicity. Patients with significant hepatic disease should use morphine cautiously due to the increased risk of adverse effects, such as CNS irritability, development of tolerance, and seizure. Intravenous and rectal routes of administration bypass hepatic metabolism, resulting in lower concentrations of metabolites compared to the oral route. Morphine's metabolites are excreted through the kidneys, so patients with renal disease may require dosage adjustments. Morphine is known to release histamine, which can lead to allergic-type reactions such as itching.[145]

Codeine

Another naturally-occurring opioid, codeine is commonly used for the treatment of pain and cough. It is available in oral formulations, as a single drug product or in combination with acetaminophen or cough medications. It is readily absorbed from the GI tract, and is metabolized in the liver by the cytochrome P450 enzymes 2D6 and 3A4; prescribers should use caution when prescribing codeine to patients with hepatic disease or in combination with medications that utilize the 2D6 and 3A4 enzymes. Codeine is primarily eliminated through the kidney, so dosage adjustments should be made in patients with significant renal disease. Similar to morphine, codeine can cause histamine release, leading to allergic-type reactions such as itching.[111,145]

Oxycodone

Oxycodone is a semi-synthetic opioid that has been used as a pain reliever for over 80 years. It is available in immediate-release and extended-release formulations, as a single drug product or in combination with acetaminophen. Oxycodone has a number of characteristics that one would want in an ideal opioid: it has few side effects, is easy to titrate, has a relatively quick onset of action and a short half-life, and its pharmacokinetics are predictable. It is metabolized by the cytochrome P450 2D6 enzyme, which converts it to oxymorphone, and the 3A4 enzyme, which converts it to an inactive metabolite. Approximately 10% of the population has lower levels of the 2D6 enzyme; these patients may require higher than average doses to achieve analgesia. Patients taking medications that are strong inhibitors of the cytochrome P450 system should be titrated on to oxycodone with caution. Oxycodone and its metabolites are excreted through the kidneys, so dose adjustment is needed in patients with renal disease.[145]

Oxymorphone

Oxymorphone is a semi-synthetic opioid that has been available since 1959 as an intravenous preparation, but was not developed into an oral product until 2006. When given intravenously, it is 10 times more potent than morphine. Oxymorphone experiences extensive first-pass metabolism, resulting in only 10% bioavailability when taken orally. However, it is more lipophilic than morphine and oxycodone, which allows it to cross the blood-brain barrier more quickly, resulting in a more rapid onset of action. After hepatic metabolism, oxymorphone is excreted through the kidney. Renal impairment can significantly increase bioavailability, so dosing adjustments are critical in patients with kidney disease. Oxymorphone is contraindicated in patients with moderate to severe hepatic impairment. Taking oxymorphone with food can significantly increase plasma concentrations, so patients should be counseled to take it on an empty stomach. Avoiding alcohol is also important, since it can increase plasma concentrations by nearly 300%.[145]

Hydromorphone

Hydromorphone is a semi-synthetic opioid that is five to six times more potent than morphine when given parenterally. It is commonly given orally and intravenously, and can also be administered by the epidural or intrathecal routes. Oral tablets are available in immediate-release and extended-release forms. Short-acting oral forms are effective within 30 minutes of administration and last for 3 to 4 hours. Intravenous hydromorphone is effective within 5 minutes. Hydromorphone is preferred over morphine in patients with renal impairment because its metabolites are produced in small quantities that have minimal accumulation.[145]

Fentanyl

Fentanyl is a synthetic opioid that is 50 to 100 times more potent than morphine. It has a relatively short half-life of 3 to 7 hours, requiring frequent or continuous administration. It is safe for use in patients with kidney disease, but is contraindicated in patients with liver failure.[111,146]

The most common formulation used in the outpatient setting is the transdermal fentanyl patch. Patients initiated on this formulation must be tolerant to opioids; it is recommended for patients taking more than 60 morphine milligram equivalents (MME) per day if they are cognitively able to apply, remove, and dispose of the patches in a safe manner. Fentanyl patches contain residual medication even after they are used for the recommended amount of time and can pose a significant safety risk to children, pets, and other family members. They should be disposed of by folding them in half with the sticky side inward and either flushed down the toilet or mixed with an unsavory substance such as used coffee grounds and sealed in a container that has a child-resistant closing mechanism.

Fentanyl is also available in sublingual and intravenous formulations, which have utility in inpatient and palliative care settings.[140,146]

Methadone

Methadone is a synthetic opioid that is used for pain and as a maintenance drug for use in the treatment of opioid addiction. Although specialized training and DEA registration is required for the treatment of addiction, any provider authorized to prescribe Schedule II controlled substances can prescribe methadone to treat pain. Over the past few decades, methadone sales have risen sharply, largely for use outside of the narcotic treatment arena. Coupled with the increase in the use of methadone for pain, questions of its safety have also been on the rise. Although methadone accounts for fewer than 5% of opioid prescriptions, it has been linked to one-third of opioid-related deaths.[147,148]

There is a disconnect between the half-life of methadone in the blood and the duration of analgesia that it provides. The plasma half-life ranges from 8 to 60 hours; the duration of methadone analgesia is 6 to 12 hours. In practice, pain relief may end long before the drug is eliminated from the body, leading to redosing and potentially dangerous systemic accumulations. Furthermore, methadone is metabolized by several different enzyme systems, subjecting it to multiple potential drug-drug interactions. The use of methadone is also complicated by its interaction with cigarette smoking, which increases the rate of its metabolism, and alcohol, which can augment its toxicity in addition to increasing the rate of its metabolism. Because of these liabilities, prescribers must exercise great caution when prescribing methadone.[111,148]

Although methadone is not commonly employed as a first-line opioid, it could be beneficial in opioid-naïve patients. Because of its slow onset and long duration of effect, it may help avoid some of the reward behaviors common to fast-acting opioids. The American Pain Society and American Academy of Pain Medicine (APS/AAPM) guidelines recommend a starting dose in most opioid-naïve patients of 2.5 mg every 8 hours, with dose increases occurring no more frequently than weekly.[111,148]

It is nearly impossible to determine an equivalent dose of methadone based on morphine dosing because the required methadone dose will decrease over time. Therefore, the lowest possible dose titration should be followed in opioid-tolerant patients. Most available narcotic equivalence tables are based on single doses. Because of its potential accumulation, relying on these charts for chronic methadone dosing can result in a substantial overdose that may not become apparent for several days.[111,148]

In 2006, the FDA issued an alert warning that methadone can cause serious cardiac conduction disturbances, including QT-interval prolongation and torsades de pointes, a potentially fatal ventricular arrhythmia.

It appears that methadone-related corrected QT (QTc) interval prolongation and cardiac arrhythmias can occur at any dose, but are more likely at higher doses, or with concomitant use of drugs that interact with methadone or that themselves prolong QTc. Although uncommon, cardiac arrhythmias that can be induced by methadone are potentially lethal if not detected. Clinicians should assess the cardiac health of patients who are candidates for methadone, paying particular attention to any history of heart disease or arrhythmias. An initial ECG may be advisable prior to starting methadone, particularly if a patient has a specific cardiac disease, or cardiac risk factors, or is taking agents that may interact with methadone.[149]

Partial Agonists

Partial opioid agonists elicit a partial response at the opioid receptors, resulting in a ceiling effect of analgesia. As a result, partial agonists are considered to have less abuse potential and are less likely to cause overdose because of a reduced ability to cause respiratory depression. Examples of partial agonists include buprenorphine and tramadol.[111,143]

Buprenorphine works as a partial agonist at the mu-opioid receptor. Because of this activity, it can be difficult to overdose on buprenorphine alone. Additionally, it can be difficult to overdose and also achieve analgesia when someone taking buprenorphine also takes an opioid agonist. This is seen as a benefit when treating addiction but can pose a challenge when treating acute pain. Since buprenorphine does have agonistic properties, albeit limited, it has some use in the treatment of chronic pain. One formulation, branded as Butrans, is a transdermal patch approved for the use of chronic pain syndromes.[111,143]

Buprenorphine is also commonly used as a treatment modality for opioid addiction. Its formulations include Subutex (sublingual) and Suboxone (a sublingual product also containing naloxone). The activity of buprenorphine at the opioid receptors is thought to decrease withdrawal symptoms, decrease drug cravings, as well as have stress-relieving and anxiolytic properties.[111,143]

Tramadol is a partial opioid agonist at the mu-opioid receptor and also prevents the reuptake of neurotransmitters serotonin and norepinephrine. Because of the additional neurotransmitter action, tramadol has numerous drug interactions with other medications that affect serotonin, such as selective serotonin reuptake inhibitors (SSRIs). This mechanism is also associated with seizures in overdose situations.[111,143]

Opioid Antagonists

Opioid antagonists block the opioid receptors and prevent any opioids with agonistic effects from exhibiting their action. They can also displace opioid agonists from their bind with opioid receptors, stopping them from exerting their action. Naloxone and naltrexone are opioid antagonists, commonly used to treat opioid overdose and in the treatment of substance use disorders.[143,150]

Choosing an Opioid

Prescribers should consider opioid therapy only if the benefits for function and pain are expected to outweigh the potential risks to the patient. If opioids are used, their use should be combined with nonpharmacologic and nonopioid therapy as appropriate to maximize the available treatment options.[118]

When starting opioid therapy in an opioid-naïve patient, immediate-release opioids should be used first at the lowest effective dosage before considering long-acting opioids.[118] Short-acting oral opioid agonists typically have a rapid effect (15 to 30 minutes) but may take longer to achieve peak efficacy because of the time required to pass the blood-brain barrier. Elimination half-lives average 3 to 4 hours, offering a relatively narrow duration of action. As a result, they are best used for acute, intermittent, or breakthrough pain.[151]

Single-agent immediate-release products are made using a variety of opioid agonists, including codeine, morphine, hydromorphone, and oxycodone. Combination products typically combine a nonopioid analgesic with an opioid, usually for use in patients with moderate pain, such as oxycodone or hydrocodone combined with acetaminophen.[152] In 2014, FDA recommended that prescribers discontinue the use of combination products containing more than 325 mg of acetaminophen per dosage unit. This decision was based on data suggesting that the increased risks of liver damage associated with larger doses of acetaminophen are not outweighed by any initial efficacy benefits.[153]

Extended-release or long-acting opioid formulations are purposely engineered to control the release of a drug in such a way as to provide relatively consistent and prolonged drug levels in the blood. The onset of action is typically slower than that of immediate-release products but offers a much longer duration of action. These potent products are typically reserved for patients suffering from chronic pain who have had previous exposure to opioids.[111,154]

Initiating therapy

Initial opioid treatment should be conducted as a trial to determine if the proposed regimen can safely and efficaciously treat your patient. An opioid trial should be pre-defined, and typically should be less than 30 days. It should only be conducted after treatment goals and a thorough treatment plan have been established. When initiating opioids, providers should:[118,155]

- Start at the lowest effective dose, and titrate up only if needed
- Initiate short-acting opioid formulations first
- Review the risks and benefits of therapy frequently, including with each dose increase
- Ensure the patient is aware of the signs of respiratory depression
- Taper doses down whenever possible
- Augment treatment with non-pharmacological and non-opioid therapy whenever possible

A decision to continue opioid therapy after an appropriate trial should be based on whether there are clinically meaningful improvements in pain and function, and if these outweigh possible risks to patient safety.[118]

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Dose titration

Patients who are opioid-naïve or have modest previous opioid exposure should be started on a low dose of a short-acting opioid and titrated slowly upward to decrease the risk of opioid-related adverse effects. If it is unclear if a patient has recently been using opioids (either prescribed or non-prescribed), the clinician should assume that the patient is opioid-naïve (i.e., not tolerant) and proceed as if opioid-naïve. Because most patients who take opioids long term start with the treatment of acute pain, prescribers should ensure the lowest effective dose is used at the beginning of acute treatment. The quantity prescribed should be no more than what is needed for the duration of pain severe enough to require opioids. As a general rule, three days or less is often sufficient, and more than seven days of opioid treatment is rarely necessary for the treatment of acute pain.[118]

Since higher dosages of opioids are associated with a higher risk of overdose and death, it is important to keep in mind the total daily dose to reduce the risk of poor outcomes. Calculating the total daily dose of opioids helps to identify patients who may require close monitoring or other measures to lower the risk of overdose. Using morphine milligram equivalents is a standardized method of calculating the total amount of opioids consumed in a day, regardless of which opioid the patient is taking. To calculate a patient's total daily dose of opioids, one must first determine the total daily dose of each opioid the patient is prescribed. Next, convert to MME by multiplying the dose of each opioid by its conversion factor. Then, add the MMEs together to determine the total MME per day. The following conversion factors are used in the calculation of MME:[156]

- Codeine: 0.15
- Fentanyl transdermal: 2.4
- Hydrocodone: 1
- Hydromorphone: 4
- Methadone
  - 1-20mg/day: 4
  - 21-40mg/day: 8
  - 41-60mg/dal: 10
  - >/= 61-80mg/day: 12
- Morphine: 1
- Oxycodone: 1.5
- Oxymorphone: 3

Prescribers should carefully evaluate the risks and benefits of increasing opiate dosages to more than 50MME per day because of the lower effectiveness of high doses and the high risk of overdosage and death. Dosages of more than 90 MME per day should be avoided unless very carefully justified.[118]

Case Study 5 Part 1

Instructions: Spend 5 minutes reviewing the case below and considering the question that follows.

Matt Davidson is a 69-year-old retired male high school physical education teacher. He has come to his primary care physician for his annual physical. He has a history of hypertension, osteoarthritis, and prostate cancer for which he was treated two years ago with a combination of external beam radiation and chemotherapy. His PSA is now near zero, and he has no signs of cancer, although he continues to be troubled by mild urinary incontinence and erectile dysfunction. On this visit, Mr. Davidson complains of joint pain, as well as a burning, tingling pain in his hands and feet. He states his pain started over 6 months ago. Last week, he had a tumble down the stairs and his pain got significantly worse. He asks if anything can be done for his symptoms.

A full evaluation of the patient's pain leads to a dual diagnosis of osteoarthritis and peripheral neuropathy secondary to chemotherapy. He rates his pain as a 7 or 8 on the 10-point scale, and reports disturbed sleep, which he says makes him more irritable during the day. He also says he no longer plays tennis, that walking has begun to hurt, and it is becoming difficult to use the computer keyboard. He takes ibuprofen several times a day but reports that this is not decreasing his pain and is giving him heartburn. He also states that he has tried taking acetaminophen around the clock as well as a topical lidocaine patch but it does not seem to be helping.

1. The provider is considering initiating an opioid for Mr. Davidson. Which of the following would be most appropriate?

A. Short-acting oxycodone tablets
B. Extended-release morphine tablets
C. Fentanyl patch
D. Buprenorphine tablets

Answer: A. If an opioid is initiated, Mr. Davidson should receive an oral short-acting opioid agonist such as oxycodone. Long-acting opioids such as extended-release morphine and fentanyl patch should be reserved for patients with severe chronic pain. This will help minimize the risk of oversedation, respiratory depression, and overdose. Buprenorphine tablets are not recommended as first-line therapy for the treatment of pain; they are indicated for the treatment of opioid use disorder.

Appropriate assessment and action: This information is used to create a treatment plan with the functional goals of: Reducing nighttime awakenings to no more than once per night; walking daily at least 1 mile without pain; and using the computer without pain. A return to tennis is left as a possible goal if less strenuous goals are achieved first. A low-dose oxycodone product is prescribed as needed for a week in conjunction with a prescription for gabapentin, as well as a prophylactic laxative (to counter the known opioid side effect of constipation). The patient receives printed information about the safe use, storage, and disposal of opioid medications.

Patients receiving more than 50MME per day should have their pain and function assessed more frequently, be considered for dose reductions if the benefits do not outweigh the risks, and be offered naloxone for overdose prevention.[156]

Abuse-deterrent formulations

Prescription drug abuse has spurred the development of novel drug formulations designed to resist various methods of tampering and misuse. Current technologies intend to make the product inactive unless taken as directed. For example, one class of deterrent formulation includes an opioid antagonist within the dosage form. If the dosage is crushed, the antagonist is released, rendering the opioid inactive. Thus, if such an ER/LA product was ground and inhaled, it would be inactive when inhaled. Another method is to use an inactive pro-drug formulation that is not activated unless subjected to gastric conditions. A third strategy is to change the physical structure of the dosage making it difficult or impossible to liquefy or concentrate the opioid. Abuse-deterrent opioid formulations, of course, do not prevent users from simply consuming too much of a medication or changing to a different opioid product.[157]

A 2010 article described the impact of an abuse-deterrent formulation of the widely abused extended-release oxycodone product OxyContin. This new formulation was designed to change the physical structure of the tablet when crushed, making it difficult to inject or inhale the medication. A total of 103 patients with an addiction to prescription opioid medications were interviewed to characterize the impact of this new formulation. The selection of OxyContin as a primary drug of abuse dropped from 35.6% to 12.8% of patients in a 21-month period. During the same period, the use of other high-potency opioids, such as fentanyl and hydromorphone, significantly increased from 20.1% to 32.3%. Interviewees had a unanimous preference for the older version of the product, and 24% devised a means to defeat the tamper-resistant properties. A total of 66% indicated that they changed to another opioid, with heroin being the most common.[158]

Periodic Review and Monitoring

If an opioid medication trial is deemed successful and opioid therapy is continued, periodic review and monitoring are recommended for the duration of treatment. Ensuring adherence to the prescribed treatment can be difficult, yet it is crucial to good outcomes. Opioid therapy is often complex and complicated by legal, social, pharmacologic, and psychological factors. Unless these issues can be overcome, safe and effective therapy may be impossible to achieve.[118,159]

Within one to four weeks of starting opioid therapy for chronic pain, prescribers should assess the risks and benefits of continuing treatment or increasing the dosage, and risks and benefits should be continually assessed every three months or less. If at any point benefits no longer outweigh the potential risks of continuing therapy, other therapies should be re-evaluated, and opioid dosages should be tapered down or discontinued.[118]

Before and periodically during opioid therapy, prescribers should reassess the risk factors for opioid-induced complications. Pain management plans should include strategies to mitigate risks such as offering naloxone to patients at a high risk of overdose, which includes patients taking more than 50 MME per day, patients with a history of overdose or substance use disorders, and those concurrently taking benzodiazepines. The patient's history of controlled substance prescriptions should be evaluated periodically using prescription drug monitoring program (PDMP) data. Depending on the patient, data evaluation can range from every prescription to every three months. Urine drug testing can also be used as a tool to prevent the diversion of opioids; testing before and periodically during long-term opioid therapy is recommended by CDC.[118]

Patients should be required to submit to urine drug screens before initiating opioid therapy and at least annually to confirm adherence to the treatment plan. Drug testing must be consensual as a part of the treatment plan, with the understanding that it is key to patient safety.[118]

Opioid Side Effects

Many patients treated with an opioid will experience side effects. Unfortunately, these side effects are challenging to manage, and tolerance to these problems frequently does not develop. Some patients can benefit from changing the opioid or the route of administration used. Proper screening, education, and pre-emptive treatment will minimize bad outcomes and enhance efficacy in many cases.[111]

Respiratory depression is the most serious adverse effect of opioids; it can be immediately life-threatening. The risk of respiratory depression or respiratory arrest is higher in patients with an upper respiratory infection, asthma, or other respiratory problems.[160] Constipation is the most common side effect but can often be managed with laxatives or stool softeners.[161] Other common side effects include sedation, dizziness, vomiting, physical dependence, tolerance, and respiratory depression. Less frequently observed side effects of opioid use are delayed gastric emptying, hyperalgesia (increased sensitivity to pain), immunologic or hormonal dysfunction, muscle rigidity, and myoclonus (spasmodic jerky contractions of groups of muscles).[160]

Opioids that have agonist effects have various immediate and long-term effects on the body. Other short-term side effects of opioids include the following:[118,144]

- Analgesia.
- Reduction of consciousness.
- Euphoria.
- Reduction in blood pressure.
- Nausea and vomiting.
- Constipation.
- Urinary retention.
- Pruritus.

Many long-term side effects of opioid agonists can be explained by hormonal dysregulation, including the following:[111]

- Depression.
- Sexual dysfunction.
- Gastroparesis.
- Hyperalgesia.
- Fractures.

Opioids and Pregnancy

Maternal opioid treatment during pregnancy is associated with a variety of birth defects that are important contributors to infant morbidity and mortality. Opioids can cross both the placenta and the blood-brain barrier, allowing for fetal exposure to opioids ingested by the mother. Maternal opioid use is associated with obstetric complications including premature membrane rupture, preeclampsia, spontaneous abortion, abruption placentae, and fetal death. Fetal opioid exposure is associated with preterm birth, low birth weight, small head circumference, and sudden infant death. Neonatal abstinence syndrome is reported frequently in newborns that were exposed to opioids in utero, which has been shown to cause behavioral, cognitive, and psychomotor impairments as the child gets older.[162]

The Nebraska Pain Management Guidance Document points out several special considerations regarding opioids and pregnancy, including:[163]

- Pregnant women are generally younger patients, who have different treatment needs and risk factors for abuse than other populations.
- A number of potentially serious adverse consequences can result from opioid withdrawal, including premature labor, membrane rupture, and fetal death
- Pregnant women may experience significant shame and guilt with their opioid use during pregnancy, resulting in a situation where the patient doesn't acknowledge the seriousness of their opioid use and leading to provider misconceptions on the severity of their addiction.
- Pregnancy causes several maternal metabolic changes, which can reduce the opioid dose needed to prevent withdrawal.
- Prolonged opioid use during pregnancy can lead to the development of neonatal abstinence syndrome, which is best treated when providers are aware of the situation before delivery.
- When treating pregnant patients for opioid-use disorder, buprenorphine is the first-line agent for treatment. Methadone has also been used for years in this population, but it is associated with a higher frequency of neonatal abstinence syndrome and opioid-related adverse effects. Obstetricians should collaborate with pain management specialists to ensure that special dosing considerations for this population are implemented.

A systematic review was conducted in 2017 to establish a better understanding of what is known about opioid use during pregnancy and birth defects. It found maternal opioid use may be linked to several congenital defects in neonates. These malformations include oral clefts, septal defects in the heart, and clubfoot. In addition, prenatal opioid exposure was also noted to be related to spontaneous abortion, premature membrane rupture, preeclampsia, neonatal abstinence syndrome, and fetal death. More research is needed to better understand the association between certain opioids and congenital defects. Due to the risk of poor outcomes for mother and baby, opioid use in pregnant women should be assessed on a case by case basis.[162].

Driving and Work Safety

Driving on opioid medications remains a controversial issue. Opioid medications may cause sleepiness, clouded thinking, decreased concentration, slower reflexes, or incoordination, all of which may pose a danger to the patient and others when driving or operating machinery; particularly at the initiation of therapy. On the other hand, several epidemiologic studies failed to show an association between long-term opioid use and motor vehicle accidents, fatalities, or citations for impaired driving. Since at least some of the cognitive and motor-impairing effects of opioids resolve with steady use and a consistent dose, some activities or driving may be allowable at the discretion of the clinician and in the absence of signs of impairment.[164]

All patients who are initially prescribed opioid medications, or those who have their dose increased, should be advised not to drive or engage in potentially dangerous work or other activities. There is no consensus on exactly how long they should abstain from driving.

Patients should be educated about the increased risk of impairment when starting opioid therapy, when increasing doses, and when taking other drugs or substances that may exacerbate cognitive and motor impairment, such as alcohol or benzodiazepines. Clinicians should be aware that certain professions, such as pilots and school bus drivers, may have restrictions on the use of opioid medications.[164]

Opioid Rotation

Opioid rotation means switching from one opioid to another to better balance analgesia and side effects. Rotation may be needed because of the development of tolerance or lack of efficacy: bothersome or unacceptable side effects; increased dosing that exceeds the recommended limits of the current opioid (for example, dose limitations of co-compounded acetaminophen); or an inability to absorb the medication in its present form (for example, 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).[165]

The choice of which opioid to switch to should be patient-specific, based on prior experience, cost, availability, and other factors. The equianalgesic dose of the new drug can be calculated using an equianalgesic dose table.[165] An example, generated by Stanford University School of Medicine, is available at https://palliative.stanford.edu/opioid-conversion/equivalency-table/.

If switching to any opioid except methadone or fentanyl, the dose of the new medication should be reduced to 25 to 50% below the calculated equianalgesic dose to reduce the risk of adverse reactions. If switching to methadone, the dose should be reduced to 75 to 90% below the calculated equianalgesic dose, due to the complicated pharmacokinetics associated with methadone and the associated high risk of overdose. If switching to fentanyl, the equianalgesic dose found in the FDA-approved manufacturer's labeling should be used. The choice of the upper or lower limit of dose reduction should be based on clinical judgment and patient characteristics.[165]

Opioids can affect patients differently, so opioid rotation must be approached cautiously, especially when converting from short acting formulations to ER/LA products. As a result, an equivalent dose table must be used carefully since variations among charts and online calculator tools can potentially result in overdose. The best opioid dose for a specific patient must be determined through cautious titration and appropriate monitoring. In some cases, because of the potential risk of harm while switching between long term opioids, it may be wise to initially use lower doses of an ER/LA opioid than what might be suggested by equianalgesic charts and, at the same time, temporarily increasing the use of a short-acting opioid if needed. The LA opioid can be gradually increased to the point where the as-needed short-acting opioid is incrementally reduced until no longer necessary.[165]

Nonadherent Patients

Patients who begin to exhibit aberrant drug-related behaviors or nonadherence to a prescription should be monitored more strictly than compliant patients. The management of chronic pain can be difficult. Putting a patient on the defensive can adversely impact their treatment. Patients presenting with complex or difficult-to-treat pain may require referral to a pain management specialist. Criteria for referral include:[119]

- Patients who continue to seek treatment for persistent, unexplained pain
- Patients with complex or high-risk pain treatment conditions, such as polypharmacy or those taking high-dose opioids
- Patients with persistent pain with significant impacts on quality of life, function, or mental health that have not responded to initial treatment by a primary care provider
- Patients with persistent neuropathic pain who failed first-line therapies
- Patients who require multidisciplinary care, such as rehabilitation, mental health treatment, and medical management
- Patients who may be candidates for interventional treatment

Patients should be referred to a psychiatrist or mental health specialist when under treatment for a co-occurring mental health disorder. Addiction specialists can assist in the treatment of patients who have chronic pain and a history of addiction. Opioid treatment programs are available for patients with opioid addiction.[118]

When referring a patient to a specialist, communicate with the specialist before the patient's first visit both verbally and with a formal referral letter to ensure continued coordination of care. Consider the affordability and insurance accepted by the recommended practice if the patient is to be compliant. It is important to encourage the patient to follow through and attend specialist appointments.[118]

Safely Halting Opioid Therapy

If at any point benefits no longer outweigh the potential risks of continuing opioid therapy, opioid dosages should be tapered down or discontinued. Opioid withdrawal symptoms can be very unpleasant but are generally not life-threatening. Weaning can be done in a number of ways, ranging from a slow 10% dose reduction per week to a more rapid 25% to 50% reduction every few days. The rate of reduction should be patient-specific and can depend on the reasoning behind discontinuing opioid therapy, medical or psychiatric comorbidities, and current dose. For example, a patient experiencing an adverse reaction may require faster tapering than others. Practitioners should consider referring patients to addiction medicine specialists when tapering is required due to aberrant behavior.[118]

If it is necessary to terminate the provider/patient relationship, clinicians must give adequate notice, support the transition by making records and discussion available to the new provider, and provide coverage for emergency treatment during the transition period. If care is discontinued without reasoning or provision for continued care, providers can be held accountable for patient abandonment.[166]

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Safe Storage and Disposal of Opioids

It is well established that many prescription drug abusers obtain them from family and friends; more than 70% of people taking opioids for nonmedical reasons obtain them from friends or family.[167] Therefore, appropriate medication disposal is an effective strategy in preventing potential abuse. Before receiving opioids, patients should be informed of these facts and provided key steps for safely maintaining their medications, including information regarding take-back programs for unneeded medications.[168]

If possible, opioid pain medications should be stored in a locked cabinet or another secure storage unit. Storage areas should be cool, dry, and out of direct sunlight. Remind patients not to store medications in their car, to keep medications in the original containers, and to avoid storing medications in the refrigerator or freezer unless specifically directed to do so by a healthcare provider or pharmacist. Medications should always be stored out of the reach of children and pets.[167]

A variety of approaches are available for home disposal of unused medications. The FDA recommends removing the drugs from their original containers and mixing them with unappealing substances, such as used coffee grounds or cat litter. Such mixes should then be sealed in a plastic bag or sealable container before placing them in the garbage. Pills should not be crushed, and never flushed down a drain or toilet, due to theoretical risks of medications polluting the water supply.[168]

Many communities sponsor take-back days for unused medications. The U.S. Drug Enforcement Agency (DEA) regularly sponsors such programs, and many communities have their own programs. Local law enforcement officials can provide information on the availability of local take-back programs or disposal sites.[168]

Opioid Patient Education

Thorough patient education about the safe use, storage, and disposal of opioid medications is an essential component of opioid prescribing best practices. This education can be partially integrated into standard patient-provider agreements or informed consent documents. As with other patient-directed materials, education must be provided in a language and at a reading level (typically sixth to seventh grade) appropriate for a clinician's patient population.[111]

Safe use of opioid medications means that patients carefully follow clinician instructions, including special directions about the timing of doses, anticipated adverse events, and whether to administer the medication with food or without. Clinicians should be mindful of any patient physical limitations, such as poor eyesight, that could interfere with the accurate and timely administration of prescribed opioids.[111]

Case Study 5 Part 2

Instructions: Spend 5 minutes reviewing the case below and considering the question that follows.

After a slight dose adjustment of the gabapentin and six months of opioid therapy, Mr. Davidson reports continued functional progress and acceptable levels of pain. He has increased his level of physical activity and reports that his mood and general health are better as a result. He says he would like to try to taper down his use of the opioid.

1. Which of the following tapering plans would be most appropriate for Mr. Davidson to use to discontinue his opioids?

A. Tapering should not be done because his pain is under control
B. His opioids should be stopped without tapering
C. He should consider a reduction of 20% per week
D. He should consider a rapid taper with a goal to discontinue within one week

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Answer: C. Since the patient states he is ready to try reducing his opioid dose, it should be attempted gradually so his pain does not rebound back and negatively impact his progress.

Appropriate assessment and action: This is a treatment success; the healthcare team should be gratified. In this case, Mr. Davidson is given clear and specific instructions on how to taper his opioid dosage to the lowest effective dosage level.

Pain Management in Terminally Ill Patients

Pain is one of the most common fears among patients with a terminal illness. A 2016 study showed that over 80% of patients who are terminally ill wish to have a pain-free death. Uncontrolled pain can cause substantial distress in both end-of-life patients and their families or caregivers.[169]

When managing severe pain in terminally ill patients, a comprehensive pain assessment should be completed initially, and pain should be reassessed frequently since end-of-life conditions can progress rapidly. Pain should be treated early in order to achieve the best possible outcomes, because it often takes longer to subside in terminally ill patients. An individualized pain management plan should be created for each patient, and pain levels as well as the presence of side effects should be monitored continually.[169]

It is common for patients with terminal illnesses to lose their ability to communicate or describe their pain over time. In the last week of life, only 43% of patients are able to communicate 5 days before their death, 28% are able to communicate 3 days before their death, and 13% are able to communicate 1 day before their death. Family members can be asked to describe if they believe the patient is in pain, but research suggests that family assessment frequently underestimates pain, resulting in inadequate pain management. Patients who are unresponsive should be observed for nonverbal signs of discomfort or pain, such as moaning or crying, facial grimacing, shaking or trembling, guarding certain areas of the body, or excessive perspiration. These signs may worsen with movement, such as positioning or turning the patient. Loss of a patient's ability to communicate at the end of life can take a significant toll on family members and caregivers, and it is critical to ensure appropriate measures are taken to manage pain throughout the process of dying.[161]

Pharmacotherapy is a critical component of pain management at the end of life, with opioids being the most commonly used class of analgesics. In addition to their potency, opioids possess mild anxiolytic and sedative properties, which can be beneficial in terminally ill patients. They are also able to be given by multiple routes of administration, which is helpful when patients lose the ability to swallow or become unresponsive. Over 75% of cancer pain patients experience adequate pain relief with opioids, showing their significant effectiveness in treating severe pain. Opioids commonly used at the end of life include morphine, fentanyl, hydromorphone, oxycodone, and methadone.[169,170]

Morphine is perhaps the most frequently used opioid in end-of-life pain management. Morphine has active metabolites that can accumulate in patients with inadequate renal clearance, so it should be avoided in those with renal failure. Accumulation can enhance the analgesic potency of morphine, leading to sedation, respiratory depression, worsening nausea, delirium, and neuroexcitability.[169,170]

Fentanyl is better tolerated in patients with poor renal function since it does not have any active metabolites. It can be administered with a transdermal patch, which is useful in patients who are unable to swallow. However, it may be difficult to titrate doses up when using the patch formulation because pain can escalate quickly at the end of life. Buccal lozenges and intravenous formulations are also available, but these routes may not be optimal for unresponsive patients at home or in nursing home settings.[169,170]

Hydromorphone also does not have significant accumulation in renal failure patients. This potent opioid is available in liquid, tablet, and suppository formulations, making it easier for patients and families to administer in both home and nursing home settings. However, frequent administration is required.[169,170]

Methadone has emerged as an ideal therapy for some end-of-life patients due to its long half-life and low cost. Its rapid distribution and slow elimination can provide great pain relief in end-of-life patients, but these same pharmacokinetics can produce oversedation easily during the beginning of therapy. In general, it is not ideal to use methadone to treat breakthrough pain, but it can be helpful to use as a longer-acting agent in conjunction with an immediate-release opioid in end-of-life patients with severe pain.[169,170]

Oxycodone, commonly used to treat pain in cancer patients, may be difficult for end-of-life patients to use due to its oral administration. In addition, it is primarily eliminated through the kidneys, so patients with severe renal disease may require dose reductions. Patients on oxycodone may require transition to subcutaneous, transdermal, or intravenous opioids to control end-of-life pain.[169,170]

Non-opioid medications can also be given to end-of-life pain patients. NSAIDs can help reduce inflammation, though their side effect profile and oral route of administration may diminish their utility at the end of life. Ketorolac can be given parenterally, but its limit of 5 days of acute administration may not be adequate for all patients. Other adjuvant medications can also be used such as antidepressants and anticonvulsants, but they are generally not available in parenteral formulations and take time to reach maximum effectiveness, limiting their use in the end-of-life setting.[169,170]

Pain Management Conclusions

Acute and chronic pain are common disease states seen by healthcare providers, and pain management can be complex and time-consuming. The pathophysiology of pain is as diverse as each patient's characterization of their experience, and to further complicate matters, there is a myriad of treatment options available. It is important for providers to thoroughly assess a patient's pain before developing an individualized, patient-specific treatment plan that often involves the use of multiple treatment modalities.

Pain management treatment regimens require regular reassessment to ensure the benefits of treatment continue to outweigh the risks, and if this balance shifts, providers should ensure treatment regimens are changed, discontinued, or referred to a more appropriate provider as the patient's condition evolves.

Introduction to Addiction

The American Society of Addiction Medicine defines addiction as a chronic medical disease that involves complex interactions among brain circuits, the environment, genetics, and a patient's life experiences. Those suffering from addiction develop compulsions to repeatedly use substances or engage in behaviors despite harmful circumstances.[171] Addiction can have immediate and long-term consequences on the patient, their family, and society as a whole. Addiction can also be costly; addiction to illicit drugs, nicotine, and alcohol costs the United States over $740 billion annually due to healthcare costs, crime, and lost productivity.[172]

Addiction is used as a term to describe the compulsion to seek drugs despite negative consequences but is not a diagnosis itself.[172] The Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) characterizes drug use diagnoses as "substance use disorders", which are subclassified into mild, moderate, or severe conditions.[173] Treatment of this complex condition can be difficult, and measures must be patient-specific and focus on several aspects of the patient's health, including medical, psychological, and social problems in addition to the drug use itself. Much effort has gone into evaluating effective treatments in an effort to decrease morbidity and mortality.[174]

Causes of Addiction

The etiology of addiction is not well understood, but research suggests it is a complex and chronic brain disorder. One widely accepted theory involves the activation of the mesolimbic dopaminergic system, known as the brain's "reward system". Addictive substances enhance the release of dopamine from neurons in the ventral tegmental area and signal reward or feelings of pleasure. Since dopamine also activates conditioning and memory mechanisms in the brain, the satisfying behaviors are reinforced and continued, and the brain becomes accustomed to this stimulation. The user may feel strong cravings for the substance, especially when surrounded by environmental factors associated with substance use. These may include stress, negative feelings, or other people who normally use with them.[175,176]

Over time, individuals can become less able to control their drug use. The brain increases motivation toward desirable behaviors involving drugs and decreases motivation for non-drug rewards that once brought pleasure; the individual's motivation to take the drug is driven by conditioned responses to signals and by negative emotional situations. This means the addict focuses on immediate reward and the high levels of dopamine released from drugs.

The constant high levels of dopamine may cause the brain to downregulate dopamine receptors and decrease its usual release. Individuals no longer feel reward from behaviors that once brought gratification because those behaviors do not release a large amount of dopamine.[175,176]

Although dopamine is a key player, it has also been suggested that glutamate, GABA, serotonin, norepinephrine, and acetylcholine are involved. Further study is needed in this area, both in biology and psychology, to find the sources of addiction.[175,176]

Beyond the brain's neurobiological mechanisms, researchers suggest a variety of risk factors may contribute to developing addiction, although they are not well understood. Genetic predisposition is one proposed risk factor for addiction or substance use disorder. Certain structural alterations in the brain, such as impairments in the reward circuitry, may increase an individual's vulnerability for addiction. Additional causes may include stress, impulsivity, mood disorders such as depression and anxiety, and other comorbid psychological issues. Another factor is environmental influences. Individuals may be trying to offset trauma or abuse, they may be surrounded by substance use by family or friends, or they may have easy access to these substances. Age can be an important factor, with a majority of those with addiction having started drug use at an early age. Additionally, some research suggests that using one addictive substance can "prime" the brain and make it more prone to becoming addicted to another substance. Having one or more of these risk factors does not mean someone will become addicted, but it does increase the odds. The more risk factors present, the greater the chance an individual will develop the disease.[177]

Substance Use Disorder

The many types of addiction defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) and referred to as "substance use disorders". Prolonged, repeated use of illicit or nonprescribed substances, such as opioids, at high doses or high frequencies can lead to substance use disorder (SUD). The Diagnostic and Statistical Manual (DSM-5) uses a list of 11 equally weighted symptoms when diagnosing substance use disorders. Patients who display fewer than two symptoms on the list are not considered to have a substance use disorder; those with two or three symptoms are considered to have mild substance use disorder; those with four or five symptoms are considered to have moderate substance use disorder; and those with six or more symptoms are considered to have severe substance use disorder, commonly referred to as addiction.[173]

The following symptoms are used in the diagnosis of substance use disorder:[173]

- Wanting to cut down or stop using a substance but not being able to.
- Using a substance for longer than intended or in larger amounts.
- Spending a lot of time getting, using, or recovering from use of a substance.
- Cravings to use a substance.
- Not managing commitments because of substance use.
- Continuing to use even when it causes relationship problems.
- Giving up important activities because of substance use.
- Continuing to use substances even when they put the patient in danger.
- Continuing to use substances even when the patient knows that he has a physical or psychological problem that may be worsened with use.
- Developing tolerance.
- Withdrawal symptoms develop when not using a substance.

According to a 2020 report from the Substance Abuse and Mental Health Services Administration (SAMHSA), an estimated 40 million Americans had a substance use disorder in the past year. However, only an estimated 4 million Americans received any substance use treatment in the past year.[178] Substance use disorders are responsible for a number of negative outcomes. Patients with drug use disorders have difficulties performing their major life tasks with both work and family. They are also at a higher risk for suicide, comorbid mental disorders, and infectious diseases such as HIV and hepatitis. Comorbid mental disorders that may occur with drug use disorder include major depressive disorder, generalized anxiety disorder, bipolar I, post-traumatic stress disorder, and other personality disorders. Infectious diseases are also a concern.[179]

Opioid Use Disorder

Within the last decade, opioid addiction has become a national epidemic, affecting people in all demographics. According to the Centers for Disease Control and Prevention (CDC), from 1999 to 2019, U.S. overdose deaths have quadrupled, and over 70% percent of overdose deaths in 2019 were attributed to opioids.[180] The Substance Abuse and Mental Health Services Administration (SAMHSA) reported in 2020 that approximately 9.5 million Americans misused opioids in 2020, and 2.7 million people had a diagnosis of opioid use disorder within the past year.[178] An estimated 70,000 Americans died from opioid overdose in 2019. The CDC reports that death rates involving synthetic opioids has increased by over 15% from 2018 to 2019, and prescription opioid death rates have decreased by approximately 7%, reflecting a change in availability and choice of opioids among users.[180]

Risk Factors

Recognizing risk factors for opioid use disorders can help providers, friends and family identify and prevent potential disease development. Risk factors for behaviors that can indicate an opioid use disorder may include:[181]

- Young age.
- Poor social support systems.
- Smoking.
- Personal or family history of substance abuse.
- History of substance abuse treatment.
- Psychological stress, trauma, or disease.
- Use of psychotropic substances.
- Sexual abuse in pre-adolescent years.
- Pain with an unclear etiology or that is exaggerated.
- Pain that results in nonfunctional status.
- Stress from uncontrolled pain.
- History of legal issues.
- Focusing on opioids or other prescription drugs.
- Childhood adversity.
- Mood swings.
- Thrill-seeking behaviors.
- Social environments that encourage illicit substance use.

Assessment for Opioid Use Disorder

When evaluating a patient for opioid use disorder, a complete history of substance use should be taken in order to evaluate the severity of the patient's condition. The history should address what substances the patient uses, how frequently they are consumed, the amount consumed, age of first use, problematic consequences associated with use, and treatment history, if any. This can help providers determine the potential severity of withdrawal symptoms and correctly diagnose the severity of opioid use disorder.[182]

Collecting information and assessing patients with a suspected substance use disorder can often be an emotional, confrontational, or stressful experience. Providers must make an effort to minimize emotional responses and prevent escalation in order to provide compassionate care. A non-judgmental, culturally sensitive environment should be utilized to encourage candid conversation between the patient and their provider. Providers are also encouraged to collaborate with other clinicians who specialize in the treatment of substance use disorder, behavioral health, care management, and psychosocial support in order to provide the best possible care to their patients.[183]

A physical examination should also be conducted in order to determine if the patient is experiencing common complications of opioid use disorder. If the patient utilizes an intravenous route of administration, callouses or scars caused by repeated injections known as track marks can be found along the course of subcutaneous veins. Examination of nasal tissue can uncover signs of intranasal insufflation of opioids such as septum perforation. Infectious signs such as lymphadenopathy, cellulitis, abscesses, and new heart murmur may also be observed. Patients who are acutely intoxicated with opioids may present with drowsiness, pinpoint pupils, slurred speech, respiratory depression, or impaired cognition. Urine drug screens can be utilized to determine the current presence of opioids or their metabolites. Opioid use disorder is diagnosed based on the criteria for substance use disorder, discussed earlier in this course.[182,184]

Treatment of Opioid Use Disorder

Treatment for opioid use disorder is evolving. Previously, treatment involved stopping opioids, managing withdrawal, and then focusing on avoiding relapse using psychosocial therapy. Psychosocial therapy was thought to help patients develop healthy habits for non-drug lifestyles. Medications were only prescribed for short-term use to ease the transition and were then discontinued. However, research has shown that short-term medication treatment is not effective; many patients will require long-term therapy.[185]

Treatment of opioid use disorder may be best conducted by specialists in addiction medicine due to the complexity of this condition. Treatment often starts with the treatment of opioid withdrawal. Patients who are physiologically dependent on opioids can experience opioid withdrawal syndrome after abruptly discontinuing or reducing the dose of opioids used. Symptoms of opioid withdrawal syndrome include tachycardia, hypertension, piloerection, mydriasis, rhinorrhea, lacrimation, insomnia, and gastrointestinal distress. This clinical syndrome is informally considered to be non-life threatening; however, opioid withdrawal can cause severe fluid loss and resultant electrolyte abnormalities that can lead to hemodynamic instability and death.[186]

The clinical time course of opioid withdrawal syndrome is typically dependent on the half-life of the opioid used. Opioids with a short half-life have a more rapid onset of withdrawal symptoms; for example, heroin has a half-life of 3 to 5 hours, and is associated with an onset of withdrawal within 12 hours of the last use. Opioids with a longer half-life, such as methadone with a half-life of up to 96 hours, can lead to withdrawal symptoms 1 to 3 days after the last use. The duration of withdrawal is also dependent on the half-life of the opioid used; heroin withdrawal typically lasts 4 to 5 days, and methadone withdrawal can last 7 to 14 days or longer.[186]

Medically Supervised Withdrawal

Medically supervised withdrawal, or detoxification, can be used on an inpatient or outpatient basis to help reduce withdrawal symptoms and safely transition the patient to a medication-assisted treatment program. This typically involves patients visiting a treatment center on an inpatient or outpatient basis for counseling, medications, and medical treatment. Medically supervised withdrawal should be incorporated as part of a comprehensive treatment program, and should not be used as a standalone treatment. People who complete detoxification and do not move on to further treatment are at a high risk of relapse, and after completing withdrawal from opioids, they often experience a lower physiological tolerance to opioids. This creates a high risk of overdose if the patient returns to using the same dosages of opioids that they were using prior to medically supervised withdrawal.[186]

Medications used in the treatment of opioid withdrawal syndrome focus on targeting the underlying pathophysiology of the condition. The euphoria produced by opioids is primarily a result of the opioid binding to the μ-opioid receptor. This binding results in a suppression of the release of norepinephrine in the locus coeruleus, causing the characteristic symptoms of sedation, decreased respiration rate, and hypotension associated with opioid intoxication. When opioids are discontinued or abruptly tapered, an increase of norepinephrine release from the locus coeruleus leads to the characteristic withdrawal symptoms of diaphoresis, lacrimation, mydriasis and tachycardia. Treatment of withdrawal focuses on these mechanisms, with μ-opioid receptor agonists and partial agonists, as well as α2 agonists, being critical elements of opioid withdrawal therapy.[186]

Buprenorphine

Buprenorphine is a partial agonist with a high affinity for the μ-opioid receptor that is used alone or in combination with naloxone for the treatment of both opioid withdrawal and opioid use disorder. Since buprenorphine partially activates the opioid receptor, it provides effective treatment for opioid withdrawal symptoms. Naloxone, an opioid antagonist, has little effect when taken orally but is often included in combination products with buprenorphine to prevent intravenous abuse of buprenorphine – if buprenorphine/naloxone is liquefied and injected, naloxone will take effect and prevent buprenorphine from activating the μ-opioid receptor. This effect is generally avoided when buprenorphine/naloxone is taken as prescribed, though a small amount of naloxone can be absorbed sublingually and displace other opioids from the opioid receptor, resulting in precipitated withdrawal in patients who have not had a sufficient amount of time pass since their last opioid dose. Patients taking methadone or other long-acting opioids may be at a higher risk of developing precipitated withdrawal. The use of buprenorphine monotherapy may be considered initially in patients taking long-acting opioids to minimize this effect, though buprenorphine monotherapy can also precipitate withdrawal due to its high affinity for the opioid receptor.[187]

Buprenorphine has a higher affinity for the μ-opioid receptor when compared to most full opioid agonists. Because of this, buprenorphine is able to displace full opioid agonists from the receptor, precipitating withdrawal on its own if insufficient time has passed since the patient's last dose of opioids. Patients with current opioid dependence should wait until mild to moderate opioid withdrawal sets in before initiating buprenorphine treatment in order to reduce the risk of precipitated withdrawal. In general, buprenorphine treatment should start at least 6 to 12 hours after the last heroin dose or 24 to 72 hours after the last dose of long-acting opioids.[187]

Initiating buprenorphine at a lower dose can reduce the risk of precipitated withdrawal. An initial dose of 2 to 4mg is recommended, followed by observation for signs of precipitated withdrawal. If withdrawal symptoms are not experienced within 60 to 90 minutes, additional doses can be given in increments of 2 to 8mg as needed.[187]

Buprenorphine has a lower risk of overdose when compared with full agonist opioids; respiratory depression is limited with a ceiling effect at higher doses. Caution is still advised, particularly when combining buprenorphine with alcohol, hypnotics, or anxiolytics, as respiratory depressive effects can be enhanced by these substances. Caution is also advised when using in patients with hepatic impairment. Buprenorphine is generally well-tolerated, but headache, anxiety, constipation, fluid retention and sleep disturbances have been reported.[187]

Unlike methadone, buprenorphine can be prescribed on an outpatient basis, with some restrictions outlined in the Drug Addiction Treatment Act of 2000 (DATA 2000). Through this act, providers can apply for waivers to prescribe certain controlled substances, such as buprenorphine, from their office settings rather than from opioid treatment programs, in order to expand access to medications to treat substance use disorders. A clinician must obtain a DATA 2000 waiver, which allows trained physicians to prescribe CIII-V medications to treat opioid use disorder in an office or clinic. The physician must have a valid medical license, a DEA number, and one additional criteria such as addiction certification, board certification in addiction medicine, or other additional training. Both buprenorphine and buprenorphine/naloxone may be prescribed with a DATA 2000 waiver. However, the DATA 2000 act limits the number of patients who can be treated at one time. The 2018 Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment (SUPPORT) for Patients and Communities Act expanded DATA 2000 to include nurse practitioners and physician assistants to increase access to treatment. More information on training and registration is available at buprenorphine.samhsa.gov.[187]

Prescribers will receive a DATA 2000 waiver identification number that begins with X. Both their DEA number and DATA 2000 waiver number must be provided on prescriptions. The "Buprenorphine Pharmacy Lookup" tool on the SAMHSA website can be used to verify a physician's DATA waiver and the number of patients they may treat at one time.[188]

Since buprenorphine can be prescribed on an outpatient basis, some additional steps are recommended to decrease diversion. The American Society of Addiction Medicine recommends frequent office visits to obtain refills, observed dosing, and pill counts, as well as urine drug screens and frequent access to state prescription drug monitoring programs. Like methadone, buprenorphine should be used in conjunction with psychosocial treatment. There are no well-established recommendations for length of therapy.[187]

Methadone

Once the mainstay of opioid withdrawal treatment, methadone is less commonly used for the treatment of withdrawal symptoms. It acts as an agonist at the opioid receptor to produce its effect, essentially acting as a replacement drug for opioids of abuse. Its slow onset of action creates less of a rewarding effect compared with other opioids, while preventing symptoms of withdrawal. Methadone is a schedule II controlled substance and can only be administered for medically supervised withdrawal at federally designated outpatient treatment programs or inpatient hospital settings. This is because if taken in high doses, methadone can cause respiratory depression and lead to an overdose, so administering the medication in a controlled environment is necessary for the treatment of withdrawal.[187]

Methadone has several unique qualities that complicate its use. It has a long half-life, which means the drug will accumulate in the body faster than it is eliminated over a 24-hour period. While this becomes less of an issue over time as drug levels reach steady state, the long half-life requires cautious dosing in the beginning of treatment to prevent overdosing. The risk of overdose is high in the first two weeks of methadone treatment, so federal law dictates that the first dose should not exceed 30mg, and the total daily dose for the first day of medically supervised withdrawal should not exceed 40mg. In general, doses should not be tapered daily – increasing at intervals of 5mg every 2 to 3 days, or 10mg every 5 days, are recommended to reduce the risk of overdose. When tapering on to methadone, patients should be carefully monitored for signs of overdose. it is important to remember that due to the long half-life, it takes time to realize the full benefits of treatment, and patients can still feel opioid withdrawal symptoms during the first few days of treatment.[187]

Maintenance doses of methadone can range from 30 to 120mg per day. Studies have shown that higher doses, such as between 80 to 100mg per day, are associated with better outcomes than lower doses. It is thought that these dosing levels create enough opioid tolerance to minimize the euphoria felt if patients decide to take additional opioids on their own.[187]

Methadone has significant adverse effects on the heart. It can prolong the QTc interval, causing potentially fatal arrhythmias such as torsades de pointes. It should not be used in patients with a pre-existing long QTc interval. It should also be used cautiously in patients with an increased risk of hypokalemia, hypomagnesemia, hypocalcemia, and bradycardia, as these can increase the risk of prolonging the QTc interval. Methadone should be avoided in combination with other medications that can prolong the QTc interval such as antipsychotics amongst others. In patients with risk factors for QT prolongation, a baseline ECG is suggested before starting methadone treatment. Similar to other opioids, methadone can cause constipation, excess sweating, drowsiness, and erectile dysfunction. Patients experiencing significant oversedation should have their dose reduced as this is a sign that their dosage may be too high.[187,189]

Methadone is metabolized by CYP2B6, CYP3A4, CYP2C19, CYP2D6 and CYP1A2. Therefore, clinicians must consider drug interactions when administering methadone. Strong CYP3A4 inhibitors, such as clarithromycin, ketoconazole and grapefruit juice, can increase effects of methadone and make a patient more susceptible to arrhythmias. Strong CYP3A4 inducers, such as rifampin and phenytoin, can decrease methadone levels and cause relapse or withdrawal.[190]

The optimal length of methadone treatment has not yet been determined, and guidelines recommend individualized treatment plans. Most patients will require chronic, possibly even lifetime treatment, to prevent relapse. Methadone treatment should also be used in conjunction with psychosocial treatment.[187,190]

Clonidine

Clonidine is an alpha-2 adrenergic agonist. Its central effect on reducing noradrenaline levels helps to reduce many symptoms of opioid withdrawal, including sweating, anxiety, intestinal cramps, diarrhea, nausea, and irritability. Clonidine is often used as an adjunctive treatment. It is frequently combined with non-narcotic medications targeting opioid withdrawal symptoms, such as non-steroidal anti-inflammatory agents (NSAIDs) for pain and ondansetron for nausea. It is also used in conjunction with buprenorphine and methadone, to treat withdrawal symptoms when tapering off of these medications. Clonidine has been shown to be more effective than a placebo but less effective than methadone or buprenorphine in decreasing the symptoms of severe withdrawal and improving treatment program retention and completion rates.[187]

Clonidine is typically given in doses of 0.1-0.3 mg every 6 to 8 hours, with a maximum recommended daily dose of 1.2mg. It is typically avoided in patients with blood pressure below 90/60mmHg, heart rate less than 60, or in patients with orthostatic hypotension. Clonidine is contraindicated in people with hypotension, pregnancy, moderate to severe kidney disease, cardiac instability, and psychosis. Adverse effects include low blood pressure and sedation, which can limit the use of clonidine.[187]

Medication Assisted Treatment (MAT)

Once withdrawal has completed, careful transition to a treatment program is recommended. Most patients with moderate to severe opioid use disorder benefit from a combination of medication and psychosocial treatment, also known as medication assisted treatment (MAT). Psychosocial treatment alone can be considered for patients who are highly motivated, have strong psychosocial supports and those with mild opioid use disorder. However, most research shows the superior efficacy of MAT with reduced substance use and higher abstinence rates when compared with psychosocial treatment alone.[191,192,193]

The end goal of medication assisted treatment is sustained, long term remission of substance use disorder. MAT has been shown to increase treatment retention, improve survival, decrease illicit opioid use and criminal activity, improve birth outcomes in pregnant women with substance use disorders, decrease the risk of bloodborne illness, and increase the ability to earn and retain employment. An integrated approach to care is recommended, with treatment intensity continuously adapting over time to the patient's changing needs.[191,194]

Adjunctive psychosocial treatment is recommended for patients with opioid use disorder. Individual or group counseling can help patients work through their treatment with licensed counselors and others who are having similar experiences. Mutual help groups are also recommended, such as Narcotics Anonymous. Selection of a mutual help group should be made carefully to ensure it is a good fit for the patient and their psychosocial needs.[192]

Buprenorphine

Buprenorphine is strongly recommended as the first line treatment MAT in patients with moderate to severe opioid use disorder. Its partial action at the opioid receptor allows for easier stabilization at the beginning of therapy while minimizing the risk of overdose. Since it does have some action at the opioid receptor, it can cause withdrawal symptoms when it is discontinued, so tapering is recommended. In addition, diversion of buprenorphine has been reported, so prescribers should utilize this medication with care and consider its use carefully in patients with a history of diversion.[187,194]

Naltrexone

Naltrexone, an opioid receptor blocker, is recommended to prevent relapse in patients who are no longer dependent on opioids. By blocking the opioid receptor, patients who relapse and use opioids while taking naltrexone experience no euphoria or effect of the opioid. Naltrexone also does not create any physiologic dependence or withdrawal symptoms when discontinued. However, it causes immediate opioid withdrawal symptoms when taken by patients who are physically dependent on opioids, so it requires the patient to be completely withdrawn from opioids before it can be initiated. This includes methadone and buprenorphine being used to treat opioid use disorder. Complete withdrawal can be difficult to achieve in patients with severe opioid use disorder, limiting the use of naltrexone.[187,194]

Naltrexone is a non-controlled medication available in oral tablets taken daily and an intramuscular formulation administered every four weeks. Poor medication adherence is a significant issue with naltrexone that often limits its use; using the injectable extended-release formulation overcomes some of these limits, but studies show adherence to this formulation is lower than buprenorphine.

If naltrexone therapy is chosen, it is preferable to start intramuscular naltrexone; when compared to placebo or no medication treatment, oral naltrexone was not found to be more effective reducing illicit opioid use or treatment retention. Starting with oral tablets may be appropriate in some cases such as highly motivated patients or in controlled settings to see if liver enzymes are affected or side effects emerge prior to committing to a longer course of treatment.[187,194]

Intramuscular injections of naltrexone are given at a dose of 380mg into the gluteal muscle every 4 weeks, though some patients, such as those who metabolize naltrexone rapidly, may benefit from increasing the frequency to every 3 weeks. Naltrexone is contraindicated in patients in acute opioid withdrawal, and should be used with caution in patients who have hepatic disease, are pregnant or breastfeeding, and those with psychiatric disorders.[187]

Adverse reactions seen with intramuscular naltrexone include nausea, fatigue, decreased appetite, and injection site reactions ranging from injection site pain to cellulitis and abscesses. Patients should be encouraged to report injection site reactions to their provider to prevent development into more serious skin conditions.[187,194]

If oral naltrexone is chosen, it is typically started at 50mg per day, though some studies have used up to 100mg per day, or started with 25mg per day for a few days and increased to 50mg once the lower dose is tolerated well. Side effects with oral naltrexone include headache, dizziness, and nausea; these tend to subside with regular use.[187,194].

Liver enzymes should be monitored within several weeks of starting either oral or injectable naltrexone, and monitored every 6 months during continued treatment due to the risk of increase with naltrexone. Naltrexone is not recommended for use in patients taking opioids, since naltrexone will decrease the effectiveness of opioids. Patients with hepatic failure or acute hepatitis should also avoid using naltrexone (ASAM, 2020b; Bruneau et al, 2018).

An important counseling point for naltrexone therapy is that patients who relapse are at an increased risked of overdose. Because they have withdrawn from opioids, they have reduced tolerance and an opioid dose they previously used could be fatal. Patients should also be counseled on the importance of adherence. Naltrexone therapy should be administered in combination with psychosocial treatment; there is no recommended length of treatment.[187,194]

Methadone

Methadone can also be used for medication assisted treatment, but federal regulations require this medication to be dispensed only from approved treatment centers, and require drug testing and diversion control, which can limit its use. In these programs, patients are seen daily for supervised dosing at the beginning of their treatment. After they are stabilized, they may qualify for take home doses of methadone to reduce their frequency of clinic visits if they meet specified requirements determined by the clinic's medical director. These can include absence of illicit drug use, participation in recovery-based activities, and productive social or occupational functioning. Stable patients may be seen less frequently per federal regulations: once weekly after six months of treatment, or once every two weeks after a year in treatment.[187]

There is not a recommended time limit for treatment with methadone. Providers should avoid using pre-determined durations of treatment due to the individualized rates of progress toward remission of opioid use disorder. Long term treatment with methadone is generally associated with better outcomes. Treatment for less than 90 days is thought to have limited effectiveness, and guidelines recommend a minimum of 12 months of treatment with methadone, though some patients may require many years of methadone treatment.[187]

Selection of Treatment and Treatment Barriers

Access to treatment is still a major issue for opioid use disorder. In a study by Yarborough, Stumbo, McCarty, Mertens, Weisner and Green[195], patients reported they were not given information on the various options for medication-assisted treatment. Others had reservations regarding using methadone because of the stigma associated with methadone clinics, and they believed methadone was extremely addictive. Based on these findings, clinicians should individualize treatment plans and fully discuss treatment alternatives with patients, along with the risks and benefits of each treatment.[195]

According to Bisaga et al.[185], although evidence supports the effectiveness of these medications, there is inadequate head-to-head data from randomized, controlled trials to support recommending one medication over another. Treatment decisions should be based on availability, insurance coverage, or patient factors or preference. Clinicians should consider the risks/benefits of treatment, side effects or drug interactions, and logistical issues.[185,187]

Overdose Management with Naloxone

Naloxone hydrochloride (Narcan) is a rapid acting competitive opioid antagonist that reverses the effects of agonistic opioids. It is able to displace opioid agonists from the mu-opioid receptor, quickly reversing the effects of opioids, including respiratory depression, sedation, and pain relief. It can be administered to patients experiencing opioid overdose via intranasal spray or by intramuscular, subcutaneous, or intravenous injection, and can be safely administered to children and pregnant patients. If the patient does not respond within two to three minutes after administration, a second dose should be administered. The duration of action of naloxone depends on the dose, route of administration, and drug overdose type. Patients who have overdosed on long-acting opioids (OxyContin, MS Contin, Kadian) typically require multiple doses or a continuous infusion of naloxone, since the opioid duration of action may be longer than naloxone's duration of action. The goal of naloxone therapy should be to restore adequate spontaneous breathing, not necessarily complete arousal.[196,197]

Naloxone is a proven safe medication. When given to patients who are not opioid intoxicated or dependent, there are no clinical effects. Even though naloxone produces a rapid withdrawal in opioid-tolerant patients, it is generally not life threatening. These symptoms are unpleasant, and some patients may become agitated and combative and require medication (e.g., benzodiazepine) to remain calm. Withdrawal symptoms include the following:[197]

- Body aches
- Diarrhea
- Tachycardia
- Runny nose
- Sneezing
- Piloerection
- Nausea
- Vomiting
- Restlessness
- Agitation
- Abdominal cramps
- Increased blood pressure

The FDA has approved injectable naloxone, intranasal naloxone (Narcan nasal spray), and a naloxone autoinjector (Evzio) for the treatment of opioid overdose. Injectable naloxone can be administered intravenously, intramuscularly, or subcutaneously in healthcare settings at doses of 0.4 mg to 2 mg every two to three minutes until respiration is restored. The Narcan nasal spray is a prefilled, needle-free device that requires no assembly. It can deliver a single 4-mg dose of naloxone into one nostril. The Evzio autoinjector is injected into the anterolateral aspect of the thigh to deliver naloxone 2 mg / 0.4 mL in a prefilled autoinjector injected either intramuscularly or subcutaneously. Once Evzio is turned on, the device provides verbal and visual guidance to the user describing how to deliver the medication, similar to automated defibrillators, in a safe, confident manner. Both Narcan nasal spray and Evzio are packaged in a carton containing two doses to allow for repeat dosing if needed. Caregivers should be advised to repeat doses in two to three minutes if no response is seen or until emergency responders arrive.[182,197,198]

Counseling Patients on Opioid Overdose Risk and Response

Evidence has shown that laypersons can learn to recognize the signs of an opiate overdose. They also can learn how to safely administer the antidote, naloxone. Naloxone kits are safe, cost effective, and reduce overdose deaths. Multiple health organizations recommend providing naloxone kits to laypersons who may witness an opioid overdose, to patients in substance abuse treatment programs, to people with substance use disorders who are leaving prison or jail, and as a component of responsible opioid prescribing.[182]

It is important to educate patients, family, and caregivers of the danger signs of respiratory depression and drug overdose. Everyone in the household should be advised to obtain immediate medical attention by calling 911 while administering naloxone intranasally, intramuscularly, subcutaneously, or intravenously if the person demonstrates any signs of overdose. Signs of opioid-induced overdose include:[182,197]

- Breathing difficulties, breathing that is slow, shallow, or not present at all, or the presence of the "death rattle"
- Hard to arouse
- Face is pale
- Skin is clammy to the touch
- Body is limp
- Fingernails or lips are blue or purple
- Person is vomiting or making gurgling noises
- Person is unable to speak, is confused, or has slurred speech
- Heartbeat is very slow or stopped

Often laypersons attempt to help the overdose victim in ways that may actually harm the person more. The health care professional should educate the layperson on the appropriate way to respond to an opioid overdose. Things that patients should be counseled to do or avoid when responding to an opioid overdose include:[197]

- **DO** call 911 for emergency medical attention upon finding a person who has overdosed.
- **DO** support the person's breathing by performing rescue breathing.
- **DO** administer naloxone as prescribed in the kit.
- **DO** turn the patient onto their side so they are in the recovery position if he is breathing independently.
- **DO** keep the person warm and don't leave them alone.
- **DON'T** try to forcefully stimulate the person, such as by slapping them, as this can cause further injury. They may be unconscious if you are unable to wake the person by shouting, rubbing your knuckles on the sternum, or lightly pinching them.
- **DON'T** put the person into a cold bath or shower. This increases the risk of falling, drowning, or going into shock.
- **DON'T** inject the person with any substance (speed, saltwater, milk, heroin). The only safe treatment for opioid overdose is naloxone.
- **DON'T** try to induce vomiting to remove drugs that they swallowed. Choking or inhaling vomit into the lungs can cause a fatal injury.

BEFORE MOVING ONTO THE NEXT SECTION, PLEASE COMPLETE CASE STUDY 6.

Benzodiazepine Use Disorder

Benzodiazepines are Schedule IV controlled substances commonly used to treat anxiety and insomnia. They work by increasing the binding of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) to the $GABA_A$ receptor, increasing its ability to exert calming effects. This effect can be helpful in the treatment of anxiety and insomnia, but has also been associated with physical dependence and addiction. In addition, when benzodiazepines are used chronically, tolerance can develop, creating a need for higher doses to achieve the same effect. Dependence can also develop with chronic use; approximately 50% of patients who use benzodiazepines for longer than one month develop dependence. Withdrawal symptoms are seen when benzodiazepines are discontinued abruptly after long term use.[199,200]

Benzodiazepine use disorder can be a chronic, relapsing condition and is associated with increased morbidity and mortality. It can involve misusing benzodiazepines that have been prescribed, as well as diversion of unprescribed benzodiazepines.[200] According to the Substance Abuse and Mental Health Administration's 2020 National Survey on Drug Use and Health, approximately 4.8 million people misused benzodiazepines in 2020, and approximately 1.2 million people were diagnosed with a sedative or tranquilizer use disorder[8].

Risk factors for developing benzodiazepine use disorder include:[200]

- Non-Hispanic white race
- Ages 18-35
- Comorbid psychiatric disorders
- Personal or family history of substance use disorder

Assessment

When evaluating patients for benzodiazepine use disorder, a complete history of benzodiazepine use, treatment, and other substance use is critical to ensuring proper treatment. Since patients can obtain benzodiazepines by prescription or illicit methods, it is important to explore both avenues. Prescription use should be reviewed to determine if the patient is adherent to their prescribed directions; evaluation of the state's Prescription Drug Monitoring Program (PDMP) can help providers identify all controlled substance prescriptions that a patient is legally prescribed in their state. Patients should specifically be asked about the type of benzodiazepines they use, the dose, the average number of tablets they consume each day, when they were last used, and the duration of use. This information can help providers evaluate the potential severity of withdrawal symptoms and the proper course of treatment.[191]

Patients should also be asked about non-prescribed and illicit substance use; if necessary, urine drug screens can be used to evaluate current drug use. The use of benzodiazepines with other sedating agents such as opioids or alcohol can increase the risk of overdose and death. The U.S. Food and Drug Administration (FDA) added a black box warning to the labels of all opioids and benzodiazepines advising against using these medications together. Because both are CNS depressants, the combination puts patients at increased risk of slowed or difficult breathing, over sedation, respiratory depression, and death. The FDA states that these medications should be prescribed together only when alternate treatments are inadequate, and dosages and durations should be kept to the minimum possible.[182]

Case Study 6

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

John is a 28-year-old patient with opioid use disorder who is starting medically supervised withdrawal. He had been using oxycodone for several years, and he recently was found unconscious after taking alprazolam and hydromorphone that he obtained illicitly in addition to his usual extended-release oxycodone dose. He is now motivated to "get his life back on track" and wants to start medication therapy. His last doses of oxycodone and hydromorphone were 72 hours ago, and he wants to begin treatment today.

1. **Which of the following treatments is strongly recommended as a first line treatment in patients with moderate to severe opioid use disorder?**
   A. Buprenorphine
   B. Naloxone
   C. Clonidine
   D. Naltrexone

Answer: A. Buprenorphine is strongly recommended as the first line treatment MAT in patients with moderate to severe opioid use disorder. Its partial action at the opioid receptor allows for easier stabilization at the beginning of therapy while minimizing the risk of overdose.

A physical examination of potential benzodiazepine use disorder patients can reveal signs of benzodiazepine intoxication, such as unsteady gait, incoordination, slurred speech, and cognitive impairment. Diagnosis of benzodiazepine use disorder is based on the diagnostic criteria for substance use disorder, discussed earlier in this course.[201]

Benzodiazepine Withdrawal

Abrupt or rapid discontinuation of long term benzodiazepine use can lead to withdrawal symptoms. Symptoms typically develop within two to three days of discontinuing short acting agents, compared with five to ten days after discontinuing longer acting agents. In general, benzodiazepine withdrawal symptoms are physical, psychological and sensory symptoms related to the state of hyperexcitability in the brain that develops after the inhibitory effects of benzodiazepines wears off. These can include:[199]

- Panic attacks
- Irritability
- Tremor
- Restlessness
- Agitation
- Sleep disturbances
- Sweating
- Difficulty concentrating
- Weight loss
- Nausea or vomiting
- Headache
- Tachycardia
- Loss of appetite
- Muscle tension, spasms, or pain

Severe cases of withdrawal can cause psychosis or seizures, which can be fatal. Seizures are more likely in patients with a history of alcohol addiction, brain damage, or abnormalities on an electroencephalogram. Other factors that can lead to more severe cases of benzodiazepine withdrawal include longer durations of benzodiazepine use before discontinuation, abrupt discontinuation after regular use, use of benzodiazepines with a shorter half-life, and use of higher benzodiazepine doses.[199]

Treatment of Benzodiazepine Use Disorder

Treatment of benzodiazepine use disorder involves tapering off benzodiazepines in a safe manner, and preventing patients from returning to benzodiazepine use after completing their taper. Many patients can successfully taper benzodiazepine use on an outpatient basis. However, inpatient treatment may be warranted for patients who have failed several tapering attempts, those taking very high doses of benzodiazepines, or those who have significant medical comorbidities that must be monitored during the taper, such as seizures.[199]

When establishing a plan for tapering benzodiazepines, providers have a choice of tapering the agent that the patient is already taking, or switching to a long-acting agent to complete the taper. Short-acting benzodiazepines are associated with more severe withdrawal symptoms, worse rebound anxiety after stopping the benzodiazepine, and higher dropout rates from discontinuation studies. Agents such as diazepam or chlordiazepoxide are commonly chosen to complete benzodiazepine tapers due to their longer duration of action.[199]

Taper rates of 25 to 50 percent every 1 to 2 weeks over a course of 6 to 10 weeks are generally recommended. Tapering schedules should be individualized based on the starting benzodiazepine dose and duration of use, as well as patient's ability to tolerate withdrawal symptoms. Patients who have used benzodiazepines for longer periods of time experience a higher likelihood of experiencing withdrawal symptoms while tapering. Patients are often recommended to follow up weekly with their providers for monitoring. If physical withdrawal symptoms are intolerable, it is recommended to return to the dose prior to the most recent reduction and slowing down the taper rate. This can help reduce withdrawal symptoms and increase the likelihood of success with the benzodiazepine taper.[199]

Adjunctive therapies to aid in tapering benzodiazepines have been evaluated, such as antidepressants and mood stabilizers. In the absence of specific comorbidities, these agents are associated with a low quality of evidence supporting their use. However, patients with comorbidities such as depression, anxiety, insomnia, or opioid use disorder should receive proper treatment of these comorbidities to aid in the success of treatment of benzodiazepine use disorder. Psychosocial interventions such as cognitive behavioral therapy (CBT) are also recommended for patients undergoing benzodiazepine tapering; studies have shown higher rates of benzodiazepine discontinuation in patients undergoing CBT when compared with tapering alone.[199]

Alcohol

Alcohol is one of the most widely used intoxicants in the world. In 2020, the National Survey on Drug Use and Health found that 50% of adults have used alcohol in the past month, and 22.2% reported drinking five or more drinks on one occasion in the past month.[178] The use of alcohol occurs on a spectrum, ranging from occasional drinking to regular, heavy use. Alcohol use disorder is a medical condition characterized by an inability to control alcohol use despite adverse consequences.[202]

Alcohol use disorder is a serious national health problem in the United States. It is estimated that more than 14 million American adults had an alcohol use disorder in 2019, as well as 414,000 adolescents aged 12 to 17.[202] There are over 95,000 deaths every year that are directly attributed to alcohol use, and the economic cost of alcohol use is astounding: excessive alcohol use in the United States is said to cost nearly $250 billion annually. The majority of these costs (77%) are associated with binge drinking, or drinking more than three alcoholic beverages per occasion for women, or more than four drinks for men.[203\]

In the United States, alcohol use disorder has a lifetime prevalence of approximately 29%. Despite the high prevalence and common complications, alcohol use disorder is undertreated. Less than 10% of patients with a diagnosis of alcohol use disorder in the past 12 months receive any treatment, and only around 6% of patients with alcohol use disorder receive evidence-based care.[204] There is a clear need for improvement in the treatment of this common condition; this course serves to review the recognition, diagnosis, and treatment of alcohol use disorder.

Short- and Long-Term Effects of Alcohol

Inebriation

Alcohol is a central nervous system (CNS) depressant, causing decreased reaction time, motor coordination, and mental performance. After ingestion, it is swiftly absorbed into the bloodstream through the stomach and small intestine. From there, it is slowly metabolized by the liver. A healthy liver typically metabolizes one standard drink per hour, which is equivalent to 12oz of 4% beer, 1.5oz of 80 proof liquor, or 5oz of table wine. The remaining alcohol continues to flow through the bloodstream until the liver is able to process it.[205]

The amount of alcohol that was consumed determines the intensity of its effect on the body. Blood alcohol concentration, or the percent of alcohol in the bloodstream, typically increases as more drinks are consumed. Blood alcohol levels of 0.08% or higher are associated with mild balance, speech, and vision impairment, and are considered too high for driving in most states. Between 0.1 and 0.15%, motor coordination and balance are significantly affected, speech may be slurred, and major loss of balance can occur. Concentrations of 0.16 to 0.3% indicate severe intoxication, causing symptoms such as confusion, nausea, vomiting, and needing assistance walking. Blood alcohol concentrations of 0.35 to 0.4% are associated with a loss of consciousness and over 0.4% can cause a coma and increase the likelihood of death by respiratory failure.[205,206]

A number of factors can impact a person's response to alcohol consumption. The presence of food in the stomach can slow the absorption of alcohol; blood alcohol concentrations can be up to three times higher in a person with an empty stomach when compared to someone who ate a meal before drinking. In addition, up to 50% of people of Asian descent are less able to metabolize alcohol due to an inactive liver enzyme needed for metabolism, resulting in more rapid intoxication, flushing, dizziness, nausea, headache, and rapid heartbeat with alcohol use. Gender can also play a significant role on the effects of alcohol. Women have less body water than men to dilute alcohol, lower quantities of the liver enzymes needed to metabolize alcohol, and the effects of estrogen can slow down the rate of alcohol elimination from the body. In addition, with chronic use, tolerance to the CNS effects of alcohol develops, so the functional impact of a specific amount of alcohol can vary.[205]

Withdrawal

Approximately 8 to 12 hours after consuming alcohol, the body's reaction to poisoning and withdrawal from alcohol, known as a hangover, begins. This reaction varies in severity based on the amount of alcohol consumed as well as individual factors, and can include headache, nausea, vomiting, fatigue, and depression. While there are a number of home remedies thought to help prevent or relieve hangovers, limiting the consumption of alcohol is the only effective remedy. Eating a full meal before drinking alcohol and alternating alcoholic drinks with non-alcoholic drinks can limit absorption.[205]

Chronically heavy drinkers who suddenly decrease or stop consuming alcohol may experience alcohol withdrawal. Alcohol withdrawal symptoms typically peak within 24 to 72 hours of the last drink, and can continue for weeks. Common symptoms include irritability, anxiety, depression, mood swings, nightmares, fatigue, and confusion. Other symptoms, such as rapid heart rate, sweating, tremor, insomnia, loss of appetite, nausea and vomiting can occur. Severe withdrawal can cause agitation, seizures, hallucinations, and delirium.[207]

Patients at risk of developing complicated alcohol withdrawal should be closely monitored. Seizures can occur within 8 to 48 hours after stopping or reducing alcohol use, with risk peaking at around 24 hours. An impending seizure can produce signs such as high blood pressure, high pulse, tremors, high temperature, or overactive reflexes, though seizures can occur without warning as well. Patients who have experienced one alcohol withdrawal seizure are at a higher risk of having another seizure or progressing to alcohol withdrawal delirium.[171]

Delirium is an acute state of confusion with impaired cognition that can occur during alcohol withdrawal. It is associated with increased morbidity and mortality, longer hospital stays, and increased utilization of health services. Prevention and early recognition are especially important in delirium management. Factors known to increase the risk of delirium include cognitive, visual or hearing impairments, immobility, dehydration, and sleep deprivation.[171]

Complications

The unhealthy use of alcohol can cause a number of medical and psychiatric complications, with higher use resulting in more profound effects. Health conditions associated with excessive alcohol use include:[208]

- Cirrhosis
- Hypertension
- Stroke
- Cardiomyopathy
- Hypogonadism
- Gastrointestinal effects such as GI bleeding, gastritis and GERD
- Osteoporosis
- Sexual dysfunction
- Chronic pancreatitis
- Brain atrophy
- Seizures
- Arrhythmias

Malnourishment is a significant issue seen with chronic alcohol use, resulting in deficiencies in vitamins A, B, and C, magnesium, folic acid, carnitine, selenium, zinc, antioxidants, and essential fatty acids. Moderate alcohol use has been associated with a higher risk of certain types of cancer, including cancers of the esophagus, larynx, mouth, liver, colon, and breast. Alcohol use is also associated with a higher risk of developing diabetes or acquiring HIV, and complicates disease state management due to the effects on medication adherence.[208]

Alcohol interacts with a number of prescription medications, including opioids, anticoagulants, anxiolytics, sedatives, and anticonvulsants. Elderly patients and patients with polypharmacy are at a particularly high risk of experiencing adverse effects from medication-alcohol interactions.[208]

Unhealthy alcohol use can also cause a number of social and mental health consequences. Depression is highly correlated with alcohol use disorders. Accidents such as falls, burns, and firearm injuries are more common among heavy drinkers, as is unsafe sex, intimate partner violence, homicide, and suicide.[208]

Alcoholic liver disease

Alcoholic liver disease covers a spectrum of liver disorders, beginning with steatosis, or fat accumulation in the liver, progressing to hepatitis, or inflammation of the liver cells, and ending with cirrhosis, or irreversible damage to the liver.[209] Signs and symptoms of liver disease can include:[171]

- Edema
- Jaundice
- Dark colored urine
- Itchy skin
- Pale, bloody, or tar-colored stool
- Chronic fatigue
- Confusion
- Nausea or vomiting

Heavy alcohol users can present with alcoholic liver disease between 40 and 50 years of age. Liver disease can be progressive; between 10 to 20% of patients with alcoholic hepatitis progress to cirrhosis each year. The management of alcoholic liver disease can vary depending on the extent of disease. Alcohol cessation is highly recommended, and patients may also require laboratory or diagnostic studies, nutritional support, regular screening for liver cancer, and treatment of complications or co-existing infections. A number of complications can arise from alcoholic liver disease, including variceal bleeding, ascites, peritonitis, renal failure, and encephalopathy.[209]

Pancreatitis

Long term alcohol use causes between 17 and 25% of cases of acute pancreatitis worldwide. This inflammatory condition affecting the pancreas causes acute abdominal pain, nausea, vomiting, anorexia, and high lipase levels. Severe cases can present with acute respiratory distress syndrome or shock. Acute pancreatitis often requires hospitalization and management with IV fluids, electrolyte replacement, analgesics and antiemetics.[210]

Between 40 to 70% of cases of chronic pancreatitis are caused by chronic alcohol use. Patients who experience recurrent cases of acute pancreatitis are significantly more likely to progress to chronic pancreatitis, in which the inflammation of the pancreas worsens over time, leads to permanent damage, and increases the patient's risk of pancreatic cancer. Chronic pancreatitis can cause the pancreas to work less efficiently, leading to poor fat absorption, steatorrhea, and diabetes. Complications of chronic pancreatitis can be local effects on the pancreas, such as necrosis and pseudocysts, as well as systemic complications such as sepsis, pleural effusion, bacteremia and shock.[210]

Screening/Assessment

Alcohol use should be assessed in patients presenting with any of the above comorbidities. When assessing a patient with suspected unhealthy alcohol use, patients should be asked about the following:[211]

- Past and current use of alcohol and any prior treatment.
- Family history of issues related to alcohol and treatment.
- Details on the quantity and frequency of use.
- Symptoms and behaviors associated with the following:
  - Alcohol use disorder criteria.
  - Medical comorbidities.
  - Behavioral complications.
  - Psychiatric complications.
  - Use of other substances.

A physical examination should be conducted to assess for features of unhealthy alcohol use. Patients may come to appointments smelling of alcohol or actively under the influence of alcohol, as noted by slurred speech, incoordination, dehydration, flushing, confusion, aggression, nausea, or vomiting. Signs of alcohol withdrawal include tremor, agitation, hypertension, diaphoresis, or clouded senses. Patients with advanced liver disease may present with hepatic enlargement, splenic enlargement, ascites, or yellowing skin or eyes:[211]

Laboratory evaluation can test for abnormalities related to heavy, repeated alcohol use or liver disease. Liver enzymes, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin and albumin, can assess for liver damage. Hemoglobin and complete blood count can determine the presence of anemia or blood dyscrasias associated with heavy alcohol use or liver disease.[211]

Patients with suspected alcohol withdrawal should have a similar assessment, with a focus on assessing recent or current withdrawal symptoms, history of prior withdrawal, and urine drug testing to rule out other substance use.

The Clinical Institutes Withdrawal Assessment Scale for Alcohol (CIWA-AR), developed in the 1980s, is a standardized evaluation tool that can be used to assess the severity of withdrawal symptoms. It can help clinicians determine the need for medically supervised withdrawal and is commonly used to guide the treatment of alcohol withdrawal symptoms. It measures the severity of alcohol withdrawal symptoms, including the following:[171]

- Nausea and vomiting.
- Headache.
- Paroxysmal sweats.
- Auditory disturbances.
- Anxiety.
- Visual disturbances.
- Agitation.
- Tactile disturbances.
- Tremor.
- Orientation and clouded senses.

Patients are scored based on symptom severity and classified as having mild withdrawal (less than 10 points), moderate withdrawal (10 to 18 points), and severe withdrawal (more than 19 points).[171]

Diagnosis

The Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) created a new diagnosis of alcohol use disorder that replaced alcohol abuse and alcohol dependence, which were described in the DSM-4. Like substance use disorders, alcohol use disorder is diagnosed when patients experience a problematic pattern of alcohol use leading to clinically significant distress or impairment.[173]

Alcohol withdrawal can be life threatening and may require intensive or inpatient care. Diagnostic criteria for alcohol withdrawal include the following:[173]

- Reduction in or cessation of alcohol use that was prolonged and heavy.
- Two or more of the following symptoms that develop within a few hours to a few days after alcohol reduction or cessation.
    - Increased hand tremor.
    - Nausea or vomiting.
    - Autonomic hyperactivity.
    - Insomnia.
    - Anxiety.
    - Generalized tonic-clonic seizures.
    - Transient hallucinations that are visual, auditory, or tactile.
    - Psychomotor agitation.
- The above symptoms cause significant distress or impairment in important areas of functioning such as social or occupational.
- The symptoms are not attributed to another medical condition, mental disorder, or intoxication or withdrawal from another substance.

Treatment of Withdrawal

Alcohol withdrawal treatment is typically dependent on the severity of withdrawal. Patients experiencing mild alcohol withdrawal, or those with a CIWA-Ar score of less than 10, can be treated by addiction specialists in the outpatient setting with supportive care alone, or supportive care and pharmacotherapy. If providing medications, carbamazepine or gabapentin are appropriate options; benzodiazepines can be given if the patient is at risk of developing new or worsening symptoms while away from the treatment center.[171]

Patients experiencing moderate alcohol withdrawal, or those with a CIWA-AR score between 10 and 18, can be treated in the outpatient setting and should receive pharmacotherapy. Benzodiazepines are considered first line treatment in these patients, though carbamazepine, gabapentin, or phenobarbital can be used as alternatives for patients with contraindications to benzodiazepines. If needed, benzodiazepines can be given with adjunctive carbamazepine, gabapentin, or valproic acid.[171]

Severe, uncomplicated cases of alcohol withdrawal, or those with a CIWA-AR score greater than 19, should be treated with pharmacotherapy. These patients can be treated in a higher-level ambulatory setting, such as a treatment program, that has regular monitoring available in the event of escalation, or in higher levels of care if necessary. Benzodiazepines should be used as first line therapy in these patients; phenobarbital, carbamazepine or gabapentin may be used as an alternative. Adjunctive therapy with carbamazepine, gabapentin, or valproic acid is also appropriate.[171]

For patients who have uncontrolled symptoms in the ambulatory setting, medication adherence should first be verified. If the patient is taking medication as prescribed, providers should consider increasing the dose. If providers are concerned about inadequate monitoring or oversedation, they can consider switching medications, adding an adjunctive medication, or reassess the level of care.[171]

Providers should consider the patient's risk for severe or complicated withdrawal when determining a treatment plan, as these patients may require closer management or inpatient hospitalization. Risk factors for severe or complicated withdrawal include:[171]

- Prior history of alcohol withdrawal seizures or delirium
- Medical or surgical comorbidities, especially traumatic brain injury
- Numerous prior episodes of withdrawal
- Age over 65 years
- Long history of regular, heavy alcohol use
- Seizures or significant autonomic hyperactivity during the current withdrawal episode
- Dependence on medications that enhance GABA such as benzodiazepines or barbiturates
- Use of other addictive substances in conjunction with alcohol
- Signs and symptoms of withdrawal in conjunction with a positive blood alcohol concentration
- Moderate to severe co-occurring psychiatric disorder

The risk of severe or complicated withdrawal is higher in patients with multiple risk factors. Providers can generally use CIWA-Ar scores to assess for the risk of severe or complicated withdrawal; patients with a CIWA-Ar score of 10 or greater, or those experiencing at least moderate alcohol withdrawal on presentation are at a higher risk of severe or complicated withdrawal. Other tools such as The ASAM Criteria Risk Assessment Matrix, the Prediction of Alcohol Withdrawal Severity Scale (PAWSS), or the Luebeck Alcohol-Withdrawal Risk Scale (LARS) can help assess a patient's risk of severe or complicated alcohol withdrawal as well as potential complications of withdrawal.[171]

Supportive Care and Nutrition

Once comorbidities and alternative substance withdrawal have been excluded, the treatment of alcohol withdrawal is focused on alleviating symptoms and correcting metabolic abnormalities. Supportive care, such as IV fluids, nutritional supplementation, and frequent clinical reassessment, is a core component of withdrawal treatment. Patients should be educated on expectations over the course of withdrawal, including common symptoms and how they will be treated. In the outpatient setting, education should be provided on monitoring for more severe withdrawal, and that safe withdrawal treatment may require transfer to a higher level of care if the ambulatory setting is not safe or effective for the patient.[171]

Patients experiencing withdrawal should be placed in a low-stimulation, reassuring environment that is calm and quiet. Dehydrated patients should receive IV fluids until they are euvolemic. Thiamine and glucose should be given to treat or prevent Wernicke's encephalopathy. Multivitamins with folate should be initiated and electrolyte disturbances such as magnesium, potassium, glucose, and phosphate should be corrected. Depending on the severity, nutritional supplementation may need to be intravenous for at least the first day or two for aspiration prevention, as well as impaired gastrointestinal absorption in patients who chronically abuse alcohol.[171,212]

Medications

Benzodiazepines

Benzodiazepines are a mainstay of alcohol withdrawal treatment. They are useful in preventing withdrawal symptoms from becoming more severe, preventing seizures and delirium, and for treating psychomotor agitation. Longer acting agents such as diazepam and chlordiazepoxide are preferrable to reduce the chance of seizures or recurrent withdrawal. Patients with severe liver disease are at a higher risk of benzodiazepine accumulation due to reduced metabolism. These patients should be treated with lorazepam because of its shorter half-life, or oxazepam because of the lack of active metabolites, which prevents prolonged oversedation. IV administration is often required in patients in severe withdrawal, for those who cannot tolerate oral administration, or those who are unconscious.

Doses vary greatly and should be patient-specific. Patients should be monitored for signs of oversedation and respiratory depression.[171]

Benzodiazepines are Schedule IV controlled substances that carry a risk of misuse or diversion. This risk can be mitigated by ordering the minimum amount needed to achieve stability and hold the patient over until their next appointment. Benzodiazepines should be discontinued once alcohol withdrawal treatment is complete. Patients and caregivers should be educated on the risks of combining alcohol with benzodiazepines, the risks of driving or using heavy machinery while taking benzodiazepines, and the interaction between benzodiazepines and other CNS depressants. Patients at a high risk of benzodiazepine abuse or diversion can be prescribed alternative medications or referred for inpatient management, depending on the severity of their case.[171]

For patients in hospitals or treatment centers, the preferred dosing method is symptom-triggered dosing administered by trained staff. In this method, patients are given medication only when experiencing significant symptoms of withdrawal, as noted by a symptom severity scale such as the CIWA-Ar, and doses are based on symptom severity. Withdrawal symptoms can be monitored using the CIWA-Ar scale every 1 to 4 hours initially, and can be extended to every 4 to 8 hours once the patient has been stabilized. Symptom triggered treatment allows for individualized dosing based on real time severity of symptoms, reducing the risk of over or under treatment. Patients may require large doses of benzodiazepines initially, with reduced doses over time. Studies have shown that symptom-triggered dosing reduces treatment duration and length of inpatient stay compared to fixed-dose schedules.[171]

Fixed dosing is commonly used in ambulatory settings. This method allows for set amounts of benzodiazepines to be administered at regular intervals, and the dose and/or frequency is gradually tapered according to a set schedule. Fixed dosing is easier for patients to self-administer, though it is also easier to over or underestimate the dose needed, leading to oversedation or sub-optimal symptom control. Patients on fixed dose schedules still require frequent monitoring, and should be reassessed regularly to determine if dosage changes are necessary.[171]

Front loading with benzodiazepines is recommended for patients in severe alcohol withdrawal, as noted by CIWA-Ar scores greater than 19. Front loading involves giving a moderate or high dose of a long-acting benzodiazepine to ensure withdrawal symptoms are rapidly controlled. Longer-acting agents such as diazepam or chlordiazepoxide are preferred agents for this purpose, to prevent the development of seizures or delirium. Studies have shown that front loading reduces the risk of withdrawal seizures, shortens treatment durations, and reduces the duration of delirium. Patients receiving front-loaded doses should be closely monitored for respiratory depression and signs of oversedation, as these side effects occur more frequently with this type of dosing regimen.[171]

Phenobarbital

Patients who have a contraindication to benzodiazepine use that are experiencing moderate to severe withdrawal, or are at risk of developing severe or complicated withdrawal, may be treated with phenobarbital. Phenobarbital, a barbiturate, was the first medication used to successfully treat alcohol withdrawal; its use for this purpose began in the 1920s. Phenobarbital is best administered by providers experienced with its use who are able to closely monitor the patient, due to the risk of toxicity when used in high doses or in combination with alcohol. Phenobarbital has a narrow therapeutic window which can create challenges in dosing it appropriately; it can cause respiratory depression and oversedation when used at high doses. Its dosing can also be complicated by its long half-life of up to seven days, and its metabolism by the liver, which can be impaired in patients who chronically abuse alcohol. Phenobarbital is associated with a number of other side effects, including hypotension, pulmonary edema, bradycardia, bradypnea, hypothermia, acute renal failure, and Steven-Johnson syndrome. When the effective use of benzodiazepines for the treatment of alcohol withdrawal was initiated in the 1960s, the use of phenobarbital fell out of favor.[171]

Anticonvulsants

Anticonvulsants such as carbamazepine, gabapentin, or valproic acid can be used as adjunct therapy with benzodiazepines to improve control of withdrawal. Carbamazepine or gabapentin can also be used as monotherapy if benzodiazepines are contraindicated; valproic acid does not have sufficient evidence to support its use as monotherapy. There is not enough evidence to support the use of anticonvulsants over benzodiazepines, particularly in patients at a high risk of severe withdrawal, delirium, or seizures. Gabapentin may be an effective adjunct bridge therapy between the treatment of alcohol withdrawal and long-term management of alcohol use disorder. Gabapentin has been associated with increased abstinence rates and fewer heavy drinking days compared with placebo in the management of alcohol use disorder. Valproic acid should be avoided in patients with liver disease as well as in women of childbearing potential.[171]

Alpha2 Adrenergic Agonists and Beta Blockers

Alpha2 adrenergic agonists such as clonidine can be useful as adjunct therapy in patients with anxiety or autonomic hyperactivity that is not controlled by benzodiazepines. Beta-adrenergic antagonists, also known as beta blockers, can also be used in appropriate patients to treat persistent hypertension or tachycardia. Since many alcohol withdrawal patients experience cardiac symptoms such as tachycardia or hypertension, those that are not alleviated by correcting electrolyte imbalances, dehydration, or through the use of benzodiazepines can benefit from the use of alpha2 agonists or beta blockers. These agents should not be used as monotherapy in withdrawal treatment: they can reduce the symptoms of withdrawal without treating the underlying pathophysiology, increasing the risk of developing more severe withdrawal. They are also not effective when used alone for the treatment of withdrawal seizures or delirium.[171]

Managing Complicated Alcohol Withdrawal

Seizures

Patients who have experienced a seizure during their current withdrawal episode should be admitted to a setting that has close monitoring available for frequent reassessment every 1 to 2 hours for the next 6 to 24 hours. Electrolyte levels should be monitored to determine the need for IV fluids and patients should be closely monitored for delirium. Safety measures such as fall precautions, frequent check-ins, and assistance with activities of daily living can also be implemented to ensure patient safety.[171]

Treatment should be initiated immediately with a medication that is effective at seizure prevention; parenteral administration through the intravenous route, or intramuscular if intravenous is unavailable, is preferred. Fast acting benzodiazepines such as lorazepam or diazepam are first line treatment. When compared to placebo in a double-blind clinical trial of emergency department patients, intravenous lorazepam significantly reduced the risk of recurrent seizures. Phenobarbital can be used in patients who are unable to use benzodiazepines; parenteral phenobarbital should only be given in intensive or critical care units due to the risk of oversedation and respiratory depression.[171]

Delirium

Patients experiencing delirium due to alcohol withdrawal often need to be admitted to intensive or critical care units to receive close nursing observation and supportive care such as regular vital sign monitoring and frequent reassessment. Intravenous access should be established quickly to allow for rapid administration of fluids and medication. CIWA-Ar scores are not recommended to monitor withdrawal symptoms in patients with delirium, since it relies on patient-reported symptoms. Instead, structured assessment scales such as the Confusion Assessment Method for ICU Patients (CAM-ICU) should be utilized. One on one observation should be initiated in patients who are agitated and disoriented. Restraints should be avoided unless necessary to prevent injury or comply with state laws.[171]

Benzodiazepines are recommended as first line treatment for alcohol withdrawal delirium. Administration of intravenous benzodiazepines to achieve a light sedation where the patient is awake but tends to fall asleep unless stimulated is recommended to help control agitation and maintain patient safety. High doses of benzodiazepines may be required to control agitation in delirium patients as compared to other populations; providers should not hesitate to use large doses, but should monitor for oversedation and respiratory depression as well. Intermittent use of long and short acting benzodiazepines is recommended; continuous IV infusion has not shown superiority over intermittent dosing and is typically more expensive.

Patients should be monitored for signs of metabolic acidosis or hyponatremia.[171]

Phenobarbital can be used as an alternative to benzodiazepines, but is not preferred due to the need for close monitoring. Adjunctive antipsychotic agents can be used if delirium and hallucinations are not controlled by benzodiazepines; antipsychotics should not be used as monotherapy due to the risk of lowering the seizure threshold and increasing the risk of withdrawal seizures. Second generation antipsychotics such as risperidone or quetiapine are preferred because they have less of an effect on the seizure threshold when compared to first generation agents. Haloperidol has also been successfully used in the management of delirium.[171]

BEFORE MOVING ONTO THE NEXT SECTION, PLEASE COMPLETE CASE STUDY 7.

Long-Term Management of Alcohol Use Disorder

Treatment of alcohol use disorder should be a collaborative process between the patient and their provider. Including the patient's family or support system can also be helpful if the patient gives permission to include them. Treatment goals should be established prior to initiating therapy and can range from reducing alcohol use, to eliminating drinking in high-risk situations, to complete abstinence. Defining goals at the beginning of therapy is associated with improved treatment outcomes.[204]

When possible, treatment for alcohol use disorder should be started concurrently with withdrawal treatment if cognitive status allows.[171] Patient preference plays a significant role in choosing therapy; some patients prefer non-pharmacological therapy, while others prefer the use of medications. Offering all available options to patients can help ensure treatment plans are developed based on patient preferences and potentially improve adherence.[204]

Pharmacotherapy for patients with moderate to severe alcohol use disorder who have a goal of abstinence or reduced consumption of alcohol and want to initiate medication treatment should begin with naltrexone or acamprosate. These medications can also be considered in patients with mild alcohol use disorder if the patient prefers medication therapy.[204]

Disulfiram can be offered to motivated patients with alcohol use disorder who have a clear goal of achieving abstinence. It is contraindicated in patients who are active alcohol users, so patients must understand the risks of consuming alcohol while taking disulfiram. Topiramate or gabapentin can also be offered as second line agents in patients who wish to reduce or eliminate alcohol consumption, those who have not responded to naltrexone and acamprosate, or who prefer to use these agents.[204]

Psychosocial interventions are recommended for all patients with alcohol use disorder. These can include alcohol counseling, motivational interviewing, couples or family therapy, social services, or participation in a mutual help group such as Alcoholics Anonymous. Psychosocial interventions can be effective to treat alcohol use disorder, but when used as monotherapy, as many as 70% of patients return to heavy drinking. Selection of psychosocial interventions should be made on a patient-specific basis.[212]

Case Study 7

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

Bill is a 48 year old combat veteran who is admitted to the hospital after a fall. He is treated for a broken leg in the emergency room, but his wife notes that her husband is a heavy drinker and that his last drink was over 24 hours ago. She says that Bill has withdrawn from alcohol several times in the past and experienced seizures and delirium on several occasions. Bill is very agitated and anxious, has a terrible headache and a tremor, and is sweating and vomiting. He also appears to be hallucinating – he is experiencing auditory and visual disturbances. The nurse administers a CIWA-AR scale and he scores a 23.

1. **Which of the following is NOT a risk factor for severe or complicated withdrawal that should be considered when developing a treatment plan for Bill?**
   - A. Age of 48 years
   - B. Long history of regular, heavy alcohol use
   - C. Numerous prior episodes of withdrawal
   - D. Prior history of alcohol withdrawal seizures or delirium

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Answer: A. Age of 48 years is not a risk factor for severe or complicated withdrawal; age over 65 years is a risk factor. Other risk factors include:

- Prior history of alcohol withdrawal seizures or delirium
- Medical or surgical comorbidities, especially traumatic brain injury
- Numerous prior episodes of withdrawal
- Long history of regular, heavy alcohol use
- Seizures or significant autonomic hyperactivity during the current withdrawal episode
- Dependence on medications that enhance GABA such as benzodiazepines or barbiturates
- Use of other addictive substances in conjunction with alcohol
- Signs and symptoms of withdrawal in conjunction with a positive blood alcohol concentration
- Moderate to severe co-occurring psychiatric disorder

2. **Bill begins to experience delirium symptoms while he is withdrawing from alcohol in the hospital and is admitted to the ICU. Which of the following is recommended as first-line therapy for the treatment of alcohol withdrawal delirium?**
   - A. Carbamazepine
   - B. Phenobarbital
   - C. Benzodiazepines
   - D. Valproic acid

Answer: C. Benzodiazepines are recommended as first-line treatment for alcohol withdrawal delirium. Administration of intravenous benzodiazepines to achieve light sedation where the patient is awake but tends to fall asleep unless stimulated is recommended to help control agitation and maintain patient safety.

Medications

Naltrexone

Naltrexone is an opioid receptor antagonist frequently used to treat opioid and alcohol abuse. It works by blocking mu opioid receptors and preventing binding, thus reducing the pleasurable effects of opioids.

It reduces alcohol consumption by modulation of opioid systems, which reduces the reinforcing effects of alcohol. Naltrexone use has been associated with a reduction in the number of drinking days, reduced likelihood of returning to drinking, and is also thought to decrease cravings. It is the drug of choice in patients with concomitant opioid use disorder, since it is approved to treat both conditions. Patients should not be actively using opioids when naltrexone is started, since it can inhibit the effects of opioids and lead to noncompliance.[204,213]

Naltrexone is available in oral tablets and an intramuscular formulation known as Vivitrol, which is administered every 4 weeks. The choice between dosage forms is based on patient preference; some patients show better adherence to daily dosages while others are more willing to attend monthly visits for injections. Typically, it is preferable to start intramuscular naltrexone to ensure adherence, though starting with oral tablets may be more appropriate in some cases, to see if liver enzymes are affected or side effects emerge, before committing to a longer course of treatment.[204,213]

Intramuscular injections of naltrexone are given at a dose of 380 mg into the gluteal muscle every 4 weeks. Adverse reactions seen with intramuscular naltrexone include nausea, vomiting, diarrhea, fatigue, decreased appetite, and injection site reactions ranging from injection site pain to cellulitis and abscesses. Patients should be encouraged to report injection site reactions to their provider to prevent development into more serious skin conditions.[204,213]

Oral naltrexone is typically started at 50 mg per day, though some studies have used up to 100 mg per day or started with 25 mg per day for a few days and increased to 50 mg once the lower dose is tolerated well. Side effects with oral naltrexone are similar to those with intramuscular naltrexone and include headache, dizziness, nausea, vomiting, diarrhea and abdominal pain; these tend to subside with regular use. Gastrointestinal side effects tend to be more common in women than in men.[204,213]

Liver enzymes should be monitored within several weeks of starting either oral or injectable naltrexone, and monitored every 6 months during continued treatment because of the risk of increase with naltrexone. Patients with hepatic failure or acute hepatitis should also avoid using naltrexone. Naltrexone is not recommended for use in patients taking prescribed opioids, since naltrexone will decrease the effectiveness of opioids. Patients should be abstinent from opioids for 7 to 14 days prior to starting naltrexone, depending on the half-life of the opioid consumed.[204,213]

Acamprosate (Campral)

Acamprosate (Campral) may be prescribed to help patients recovering from alcohol abuse or dependence to help decrease alcohol cravings and relieve emotional discomfort. Acamprosate's action in alcohol use disorder is through modulating excitatory glutamate neurotransmission and enhancing GABA, which may help reduce alcohol cravings.

It has been shown to significantly reduce the risk of returning to alcohol use after achieving abstinence and reducing the number of drinking days. It is an effective first-line alternative to naltrexone and is often chosen in patients taking opioids and those with severe liver disease. It is also a useful second-line treatment in patients who do not experience an adequate response to naltrexone.[204,213]

Dosing for acamprosate is 666 mg tablets three times daily. Patients with moderate renal dysfunction, shown by a creatinine clearance of 30 to 50 ml/min, are recommended to begin at 333 mg three times daily. Lower dosing can also be considered for patients with a body weight less than 60 kg. Acamprosate is generally well tolerated; common side effects include nausea and diarrhea and, although rare, depression and suicidality. Renal function should be monitored; acamprosate is contraindicated in those with creatinine clearance less than 30 mL/min. There are no known drug interactions. Healthcare providers should counsel patients on the importance of adherence to acamprosate to ensure its effectiveness.[204,213]

Choosing between Naltrexone and Acamprosate

A number of factors can be considered when deciding between initiating naltrexone and acamprosate in a patient with alcohol use disorder. These include available formulations, ease of administration, side effects and presence of renal or hepatic disease. A large meta-analysis did not show a statistically significant difference between acamprosate and naltrexone in the percent of patients with a return to drinking, percent of patients with a return to heavy drinking, or the number of drinking days. Therefore, naltrexone or acamprosate can be seen as an appropriate initial treatment for alcohol use disorder, and patient-specific factors should be utilized to determine the best choice for a given patient.[204]

Disulfiram (Antabuse)

Disulfiram (Antabuse) is prescribed to help dissuade patients from drinking. Disulfiram works by inhibiting aldehyde dehydrogenase, the enzyme involved in metabolism of the primary metabolite of alcohol, acetaldehyde. If alcohol is consumed in the presence of disulfiram, acetaldehyde levels increase to toxic levels, creating very unpleasant side effects including nausea, vomiting, flushing, headache, dyspnea, palpitations, lowered blood pressure, and sympathetic overactivity. Symptoms typically begin within 10 minutes of consuming alcohol, and the severity of the reaction is typically related to the amount of alcohol ingested. Symptoms can last for several hours or up to a day. Some patients develop more severe reactions such as chest pain, seizures, confusion, headache, or severe vomiting; these require further evaluation to rule out alternative conditions such as myocardial infarction.[204,213]

Disulfiram is typically given in doses of 125 to 500mg per day. Disulfiram should not be administered to patients who are currently drinking or intoxicated with alcohol. Patients must be clearly informed about the effects of the drug and give permission for its use; this treatment's effectiveness depends on the patient's cooperation. Patients should be educated on hidden forms of alcohol, such as that found in mouthwash, and that the medication can continue to exert its effects for up to 14 days after discontinuation. Adherence can be a significant issue with disulfiram use; enlisting the help of a family member, roommate, or other support person can help keep the patient accountable.[204,213]

Disulfiram is often reserved for second line therapy in patients with alcohol use disorder. Naltrexone and acamprosate appear to have more evidence of benefits with their use, and disulfiram has a number of physiological consequences if alcohol relapse occurs. However, some patients who have a clear goal of abstinence prefer the accountability that disulfiram requires. Studies have not shown high-strength evidence on the benefits of disulfiram, but it appears to have a clear role in motivated patients.[204]

Disulfiram is contraindicated in patients with psychosis, clinically significant coronary artery disease, and known hypersensitivities to the medication. When alcohol is avoided, disulfiram is generally well-tolerated, but side effects may include drowsiness, metallic taste and headache. Serious side effects are rare but can include psychosis and hepatitis. Patients should have a hepatic panel drawn a few weeks after initiating treatment and repeat every 6 months with continued treatment. Patients with seizure disorders should avoid disulfiram due to the potential for seizures when alcohol is consumed while taking disulfiram.[204,213]

Drug interactions with disulfiram include the following:[213,214]

- Isoniazid: Can increase serum concentrations of isoniazid. Avoid concurrent use.
- Metronidazole: May cause psychotic reaction because of the increased effects of both disulfiram and metronidazole. Avoid concurrent use.
- Phenytoin: May increase toxic effect of phenytoin. Phenytoin levels must be carefully monitored, and dose adjusted as needed.
- Warfarin: Disulfiram can increase the concentration of warfarin; therapy adjustments may be required.

An important counseling point for disulfiram is for the patient to avoid any type of alcohol-containing product, even mouthwashes and cough syrups. These products may cause the unwanted reactions if taken while using disulfiram. Patients should also be counseled that if they do drink alcohol, fatal hypotension can occur. Reactions with alcohol ingestion may occur up to two weeks after disulfiram is stopped.[204,213]

Topiramate (Topamax)

Topiramate is an anticonvulsant that affects voltage-dependent sodium channels, GABA transmission, and glutamate receptors. It has been found to reduce alcohol use in patients with alcohol use disorder and is the preferred second-line option in patients with seizure disorders.

Some have shown that topiramate has mild to moderate effectiveness in reducing the percent of drinking days, reducing heavy drinking days, increasing abstinence, reducing cravings, and improving quality of life, but results have not been consistent in displaying these outcomes.[204,213]

Topiramate is initiated at 25 mg daily and can be titrated up slowly over 8 weeks to a maximum dose of 300 mg per day; titration helps to minimize the risk of adverse effects. Adverse effects associated with topiramate include cognitive impairment, sedation, weight loss, gastrointestinal side effects, headache, fatigue, dizziness, depression, and paresthesias. Since weight loss occurs in 4 to 21% of patients, topiramate may be preferrable in obese patients. Some patients find the cognitive impairment associated with topiramate to be intolerable, as it affects word finding abilities and can impact psychosocial interactions. Rare but serious side effects include nephrolithiasis, acute angle-closure glaucoma, and metabolic acidosis. It may be beneficial to monitor renal function and cognitive status prior to initiation.[204,213,215]

Gabapentin (Neurontin)

Patients who previously failed first-line treatments can consider gabapentin for alcohol use disorder. Gabapentin is an anticonvulsant that is structurally similar to GABA and may modulate excitatory neurotransmitters in the brain; it can be used off-label for alcohol use disorder. Clinical trials showed that doses of 900 to 1800 mg per day have shown efficacy in reducing the percentage of heavy drinking days, increasing abstinence rates, reducing drinking frequency and quantity, and improving mood, cravings, and sleep. Common side effects associated with gabapentin include dizziness, drowsiness, fatigue. Gabapentin is primarily eliminated through the kidneys, and patients with renal impairment require dosage adjustments. There have been reports of addictive potential with gabapentin; providers should be alert to potential misuse.[204,216]

Psychosocial Therapy

Along with any of these medications, one or more psychosocial interventions are recommended, including cognitive behavioral therapy, behavioral couples therapy, community reinforcement or group therapy, motivational enhancement therapy, and 12-step programs While the quality of evidence supporting these interventions is low, they can modestly improve adherence, reduce alcohol consumption, and assist in recovery of patients with alcohol use disorder, particularly when used in combination with one another or with pharmacological therapy.

Psychosocial therapy may be particularly beneficial in patients with co-occurring mental health conditions such as anxiety or depression.[216]

Cognitive behavioral therapy (CBT) helps patients adjust their behavior and thinking related to alcohol use and encourages patients to change other areas of life that are related to their alcohol use. Patients are taught to track activities and thinking in order to identify the consequences, such as alcohol use episodes and cravings. Then techniques are taught to help the patient change behaviors and thoughts that contribute to alcohol use in order to improve interpersonal functioning, mood, coping skills, and social support. Treatment plans include structured practice outside of therapy sessions, such as self-monitoring, scheduled activities, thought recording and practicing interpersonal skills. Cognitive behavioral therapy has been shown to be effective in patients with alcohol use disorders compared to minimal psychosocial interventions.[216]

The community reinforcement approach is a type of cognitive behavioral therapy that focuses on environmental factors that influence the patient's behaviors. Environmental factors can be greatly influential on a patient's addictive behavior, so this approach uses social, recreational, family and occupational events to support the patient in changing their behavior. This helps the patient develop healthy behaviors that allow a sober lifestyle to become more rewarding than one that involves alcohol use. Some forms of the community reinforcement approach provide incentives for positive behaviors, such as taking medication, attending treatment sessions, or abstinence.[216]

Behavioral couples therapy is useful for patients in relationships, and focuses on reducing alcohol use and improving relationship satisfaction for both the patient and their partner. Shared activities and behavioral assignments are given to help increase positive feelings and communication between partners. Behavioral couples therapy has been shown to improve marital satisfaction, and improving relationship functioning is conducive to sobriety, therefore patients with motivated partners can benefit from this intervention.[216]

Motivational enhancement therapy is a less intensive psychosocial intervention that utilizes motivational interviewing to elicit patient reactions to feedback, help patients commit to change and collaborate on a plan to change their behavior. It helps improve the patient's awareness of their own ambivalence about changing their behaviors and enhances their self-efficacy. Patients are encouraged to involve a significant other in at least one session in order to improve outcomes.[216]

Twelve-step facilitation therapy is utilized to help the patient become more actively involved in Alcoholics Anonymous (AA) or other 12-step programs. It involves 12 sessions of individual therapy, encouraging the use of AA and helping the patient understand the steps of the AA program. Sessions are structured and are spent reviewing events of the past week related to recovery, introducing material related to the 12 steps, and creating a homework assignment and developing a plan for the next week's recovery-related activities. Twelve-step facilitation therapy has consistently improved participation in 12-step programs and produced significant improvements in some drinking outcomes such as abstinence when compared to cognitive behavioral therapy or motivational enhancement therapy.[216]

Addiction Conclusion

Patients who suffer from substance use disorders have a number of hurdles to overcome in their road to recovery. Regardless of the severity of their condition, most patients will require customized treatment based on patient factors, preferences, and comorbid disease states. Many patients will require more than one attempt at quitting, and healthcare providers can offer guidance, motivation, and support throughout their journey.

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UNDERSTANDING AND COMPASSION: PAIN, ADDICTION AND END-OF-LIFE CARE

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. Roughly how many American adults have created an advance directive?

A. One in two.
B. One in three.
C. One in four.
D. One in five.

22. How accurate are physicians, generally, in predicting patient preferences for end-of-life care?

A. About 55% accurate.
B. About 65% accurate.
C. About 75% accurate.
D. About 85% accurate.

23. In the United States, what term is generally used for care of people who are not expected to live more than 6 months?

A. Palliative care.
B. Nursing home care.
C. Hospice care.
D. Terminal care.

24. The Karnofsky Scale may be useful for what clinical task?

A. Assessing patient's cognitive ability.
B. Determining level of adverse effects associated with chemotherapy.
C. Determining patient pain level.
D. Determining patient life expectancy.

25. Which statement is true about the typical role of a referring physician relative to patients in hospice care?

A. Hospice staff are expected to be in charge of patient care, with a referring physician consulted only for prescription refills.
B. The referring physician is expected to remain in charge of care and be available by phone or other means.
C. The referring physician transfers responsibility for patient care to the hospice medical director.
D. The hospice team assumes responsibility for all patient care, including the ordering and administration of prescription medications as needed.

26. Which of the following forms of patient expressed end of life wishes are legally enforceable?

A. Advance Directive.
B. Living Will.
C. POLST.
D. Living Trust.

27. The opioids butorphanol, nalbuphine, and pentazocine, are not recommended in cancer pain management because _____.

A. They are likely to cause psychotomimetic effects.
B. They are associated with an increased risk of pruritus.
C. They commonly cause severe constipation.
D. Their metabolites may be neurotoxic in the context of chemotherapy.

28. Unwarranted fear of what potential side effect of opioid analgesics can lead to underprescribing by clinicians and/or under use by patients?

A. Respiratory depression.
B. Sedation.
C. Nausea.
D. Constipation.

29. Which class of adjuvant analgesic has received increasing attention in recent years as a possible way to control neuropathic pain?

A. Tricyclic antidepressants.
B. Cannabinoids.
C. Psychostimulants.
D. Ketamine.

30. Which class of medications are first-line for treating dyspnea in end-of-life settings?

A. Corticosteroids.
B. Benzodiazepines.
C. Bronchodilators.
D. Opioids.

31. Which of the following is an advantage of using function-based goals in pain management?

A. The patient's perceived pain levels are not the primary focus of treatment.
B. Prescribing decisions are based on the patient's subjective pain experience.
C. Function-based goals require lower doses of opioids.
D. Progress can be measured quickly when using function-based goals, over the course of several hours.

32. Which of the following is recommended by the American College of Physicians as a first-line non-pharmacological treatment for chronic low back pain?

A. Meditation.
B. Acupuncture.
C. Deep breathing.
D. Massage.

33. Both chronic and short-term use of _____ is associated with an increased risk of myocardial infarction or stroke.

A. Acetaminophen.
B. Gabapentin.
C. NSAIDs.
D. Cyclobenzaprine.

34. Which of the following is a partial agonist at the mu-opioid receptor?

A. Tramadol.
B. Fentanyl.
C. Methadone.
D. Naloxone.

35. It may be difficult to titrate doses up when using _____ because pain can escalate quickly at the end of life.

A. Liquid morphine.
B. Fentanyl patches.
C. Intravenous hydromorphone.
D. Buccal fentanyl lozenges.

36. Which of the following is a symptom used in the diagnosis of substance use disorder?

A. Wanting to cut down or stop using a substance and being able to.
B. Using a substance for shorter time than intended or in smaller amounts.
C. Giving up substance use, particularly when it causes relationship problems.
D. Continuing to use substances even when they put the patient in danger.

37. Which of the following treatments for opioid use disorder is a schedule II controlled substance that can only be administered for medically supervised withdrawal at federally designated outpatient treatment programs or inpatient hospital settings?

A. Methadone.
B. Buprenorphine.
C. Naloxone.
D. Naltrexone.

38. If a patient were to experience an opioid overdose, all of the following symptoms would be likely related to overdose EXCEPT?

A. Slow or shallow breathing.
B. Clammy skin.
C. Fast heart rate.
D. Blue or purple lips.

39. All of the following are associated with more severe cases of benzodiazepine withdrawal EXCEPT:

A. Longer durations of benzodiazepine use before discontinuation.
B. Abrupt discontinuation after regular use.
C. Use of benzodiazepines with a longer half-life.
D. Use of higher benzodiazepine doses.

40. Which of the following benzodiazepines is preferred in alcohol withdrawal patients who do not have severe liver disease?

A. Alprazolam.
B. Lorazepam.
C. Temazepam.
D. Diazepamv.

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

Alternatives to Opioids for Pain Management

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

Effective Management of Acute and Chronic Pain with Opioid Analgesics

	A	B	C	D
11	○	○	○	○
12	○	○	○	○
13	○	○	○	○
14	○	○	○	○
15	○	○	○	○
16	○	○	○	○
17	○	○	○	○
18	○	○	○	○
19	○	○	○	○
20	○	○	○	○

Understanding and Compassion: Pain, Addiction and End-of-Life Care

	A	B	C	D		A	B	C	D
21	○	○	○	○	31	○	○	○	○
22	○	○	○	○	32	○	○	○	○
23	○	○	○	○	33	○	○	○	○
24	○	○	○	○	34	○	○	○	○
25	○	○	○	○	35	○	○	○	○
26	○	○	○	○	36	○	○	○	○
27	○	○	○	○	37	○	○	○	○
28	○	○	○	○	38	○	○	○	○
29	○	○	○	○	39	○	○	○	○
30	○	○	○	○	40	○	○	○	○

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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 - ALTERNATIVES TO OPIOIDS FOR PAIN MANAGEMENT:

		A	B	C	D
1.	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.	○	○	○	○
2.	Appropriately prescribe the full range of non-opioid analgesic options for managing acute and chronic non-cancer pain	○	○	○	○

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

_____

4. What do you see as a barrier to making these changes? _____

_____

COURSE 2 - EFFECTIVE MANAGEMENT OF ACUTE AND CHRONIC PAIN WITH OPIOID ANALGESICS:

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

7. Please identify a specific change, if any, you will make in your practice related to safe prescribing of opioid analgesics. _____

_____

8. What do you see as a barrier to making these changes? _____

_____

COURSE 3 - UNDERSTANDING AND COMPASSION: PAIN, ADDICTION AND END-OF-LIFE CARE:

		A	B	C	D
9.	Manage patients at the end-of-life in ways consistent with their stated preferences and appropriately manage patients in hospice.	○	○	○	○
10.	Evaluate patients in pain and develop a comprehensive treatment plan.	○	○	○	○
11.	Utilize both non-pharmacological and pharmacological treatment modalities to manage pain.	○	○	○	○
12.	Identify addiction disorders and develop patient-specific treatment options.	○	○	○	○

13. Please identify a specific change, if any, you will make in your practice related to pain, addiction and end-of-life care. _____

_____

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?

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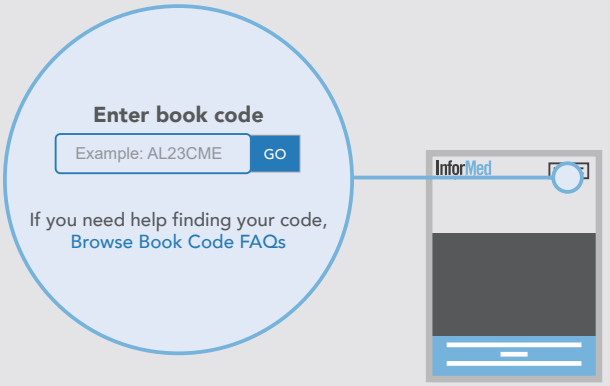

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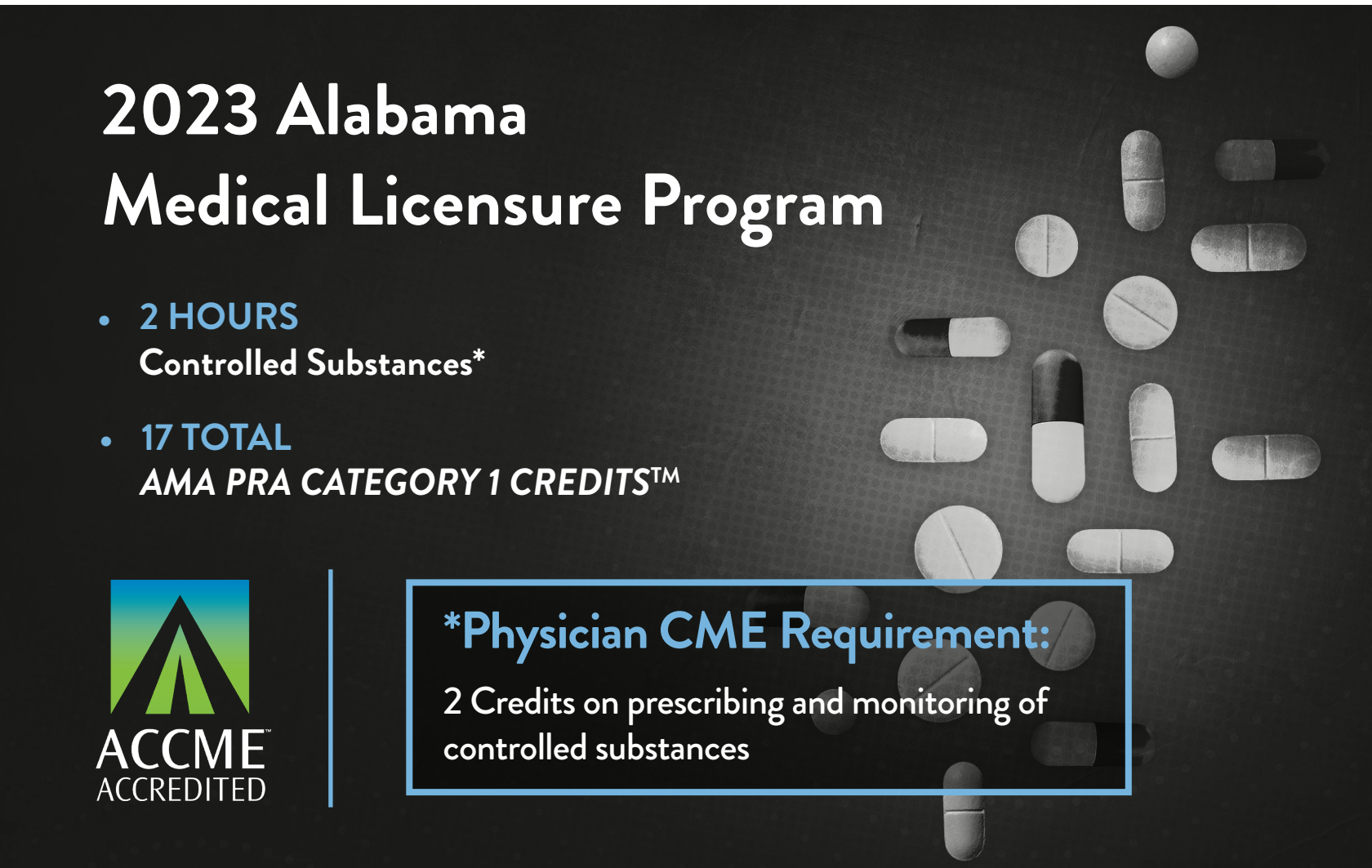

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ACCME ACCREDITED

***Physician CME Requirement:**

2 Credits on prescribing and monitoring of controlled substances

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

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