

2023 California Medical Licensure Program

- **12 HOURS**
Pain Management and
Appropriate Treatment of
the Terminally Ill*



***Mandatory CME Requirement:**
12 Hours pain management and appropriate
treatment of the terminally ill.

CME FOR:

AMA PRA CATEGORY 1 CREDITS™

MIPS

MOC

STATE LICENSURE

CA.CME.EDU

2023 CALIFORNIA

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

12 CREDITS*

Satisfies twelve (12) credit CME requirement in pain management and the treatment of terminally ill and dying patients.

48 LEARNER RECORDS: ANSWER SHEET & EVALUATION REQUIRED TO RECEIVE CREDIT



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.

\$135.00

**PROGRAM PRICE
(12 CREDITS)**

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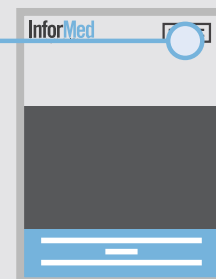
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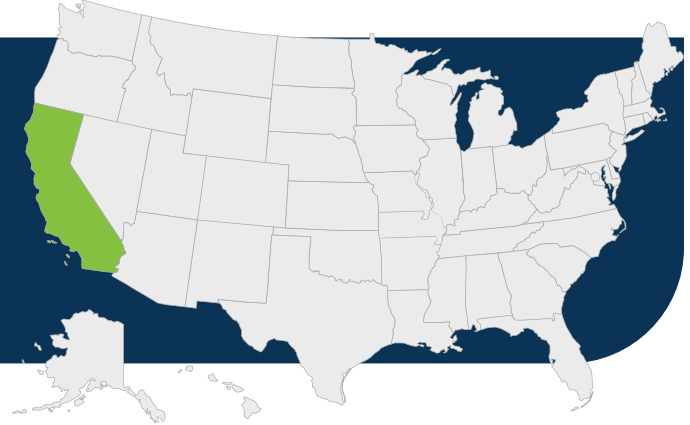
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California Professional License Requirements

PHYSICIANS

MANDATORY CONTINUING MEDICAL EDUCATION REQUIREMENT FOR LICENSE RENEWAL

PAIN MANAGEMENT/TERMINALLY ILL PATIENTS

The Medical Board of California requires all physicians (excluding pathologists and radiologists) to earn twelve (12) credits of continuing education in pain management and the treatment of terminally ill and dying patients (business and professions code §2190.5). Physicians must complete this one-time requirement by the second renewal of their medical license or four (4) years from the date of their initial license, whichever occurs first. When earned, these credits count toward the total hours required during that biennium.

OTHER PHYSICIAN CME REQUIREMENTS

The Medical Board of California requires 50 *AMA PRA Category 1 Credits*[™] of continuing medical education credits each biennium as a prerequisite for physicians to renew their medical license. Also, under California's law, the Medical Board requires that all general internal medicine and family practice physicians, that have a patient population of which 25 percent are age 65 years or older, complete at least 20 percent of their 50 credits each biennium in the field of geriatric medicine.

What This Means for You:

You must earn the mandatory twelve (12) hours in pain management and the appropriate treatment of terminally ill and dying patients before your second renewal or four years from the date of your initial license, whichever occurs first.

LICENSE RENEWAL INFORMATION

**50 AMA PRA CATEGORY 1 CREDITS[™] including
12 CREDITS in Pain Management/Terminally Ill***

**One-time mandatory CME requirement*

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

Medical Board of California
2005 Evergreen Street, Suite 1200
Sacramento, CA 95815
Email: webmaster@mbc.ca.gov
P: 1-800-633-2322

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

MOC/MIPS CREDIT INFORMATION

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

Table 1. MOC Recognition Statements

Successful completion of certain enclosed CME activities, which includes participation in the evaluation component, enables the participant to earn up to the amounts and credit types shown in Table 2 below. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting MOC credit.

Board Programs

	ABA	American Board of Anesthesiology's redesigned Maintenance of Certification in Anesthesiology™ (MOCA®) program, known as MOCA 2.0®
	ABIM	American Board of Internal Medicine's Maintenance of Certification (MOC) program
	ABO	American Board of Ophthalmology's Maintenance of Certification (MOC) program
	ABOHNS	American Board of Otolaryngology – Head and Neck Surgery's Continuing Certification program (formerly known as MOC)
	ABPath	American Board of Pathology's Continuing Certification Program
	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
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.

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

COURSE DATES:	MAXIMUM CREDITS:	FORMAT:
Release Date: 1/2023 Exp. Date: 1/2026	12 <i>AMA PRA</i> <i>Category 1 Credits™</i>	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.

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.

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.

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.

ACCREDITATION STATEMENT

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

DESIGNATION STATEMENT

InforMed designates this enduring material for a maximum of 12 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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DISCLOSURE OF INTEREST

In accordance with the ACCME Standards for Integrity and Independence in Accredited Continuing Education, 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 relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients:

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STAFF AND CONTENT REVIEWERS

InforMed staff, input committee and all content validation reviewers involved with this activity have reported no relevant financial relationships with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

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COURSE SATISFIES



SPECIAL DESIGNATION

This course satisfies twelve (12) CME credit hours on pain management and the appropriate treatment of the terminally ill.

The Medical Board of California requires most physicians and surgeons to complete a one-time mandatory 12 hours of CME in the subjects of pain management and the treatment of terminally ill and dying patients.

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 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. 8). Skillful delivery of bad news can provide comfort for the patient and family.

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Table 2. Components of individualized EOL care²

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 to 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-maleficence (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 news²⁴

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 Scale³²

- National Hospice Organization Medical Guidelines for Determining Prognosis in Selected Non-Cancer Diseases³³
- Palliative Performance Scale³⁴
- Palliative Prognosis Score³⁵

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 care³⁰

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.

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.

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

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-naïve 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 oxycodone 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 Management⁵⁶

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	IV IV	Pain flare, osteonecrosis	Osteolytic bone pain
	Clodronate			
	Alendronate			
	Zoledronic acid			
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 symptoms⁷²

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 Scale⁸⁵ 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-HT₃ 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 patients³⁶

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 use¹⁰²
- 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 Caregivers¹⁰⁴

- 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 than 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

- **Site:** Where exactly is the pain?
- **Onset:** When did it start? Was it constant or intermittent? Was it gradual or sudden?
- **Character:** What is the pain like? Sharp? Burning? Tight?
- **Radiation:** Does the pain radiate or travel anywhere?
- **Associations:** Are there any symptoms associated with the pain such as sweating or vomiting?
- **Time course:** Does it follow any time pattern? How long does it last?
- **Exacerbating and relieving factors:** Does anything make it better or worse?
- **Severity:** 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 include¹³⁶:

- 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 include¹³⁷:

- 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 include¹⁴⁰:

- 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 concerns¹⁴²:

- 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
 - \geq 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

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 oversaturation 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 $\alpha 2$ 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 risk 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 Green¹⁹⁵, 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 ON TO 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 disorder⁸.

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 preferable 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 ON TO 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

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 preferable 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.

- 1. 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.
- 2. 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.
- 3. 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.
- 4. 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.
- 5. 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.
- 6. 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.
- 7. 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.
- 8. 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.
- 9. 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.
- 10. Which class of medications are first-line for treating dyspnea in end-of-life settings?**
 - A. Corticosteroids.
 - B. Benzodiazepines.
 - C. Bronchodilators.
 - D. Opioids.
- 11. 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.
- 12. 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.

13. Both chronic and short-term use of _____ is associated with an increased risk of myocardial infarction or stroke.
- Acetaminophen.
 - Gabapentin.
 - NSAIDs.
 - Cyclobenzaprine.
14. Which of the following is a partial agonist at the mu-opioid receptor?
- Tramadol.
 - Fentanyl.
 - Methadone.
 - Naloxone.
15. It may be difficult to titrate doses up when using _____ because pain can escalate quickly at the end of life.
- Liquid morphine.
 - Fentanyl patches.
 - Intravenous hydromorphone.
 - Buccal fentanyl lozenges.
16. Which of the following is a symptom used in the diagnosis of substance use disorder?
- Wanting to cut down or stop using a substance and being able to.
 - Using a substance for shorter time than intended or in smaller amounts.
 - Giving up substance use, particularly when it causes relationship problems.
 - Continuing to use substances even when they put the patient in danger.
17. 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?
- Methadone.
 - Buprenorphine.
 - Naloxone.
 - Naltrexone.
18. If a patient were to experience an opioid overdose, all of the following symptoms would be likely related to overdose EXCEPT?
- Slow or shallow breathing.
 - Clammy skin.
 - Fast heart rate.
 - Blue or purple lips.
19. All of the following are associated with more severe cases of benzodiazepine withdrawal EXCEPT:
- Longer durations of benzodiazepine use before discontinuation.
 - Abrupt discontinuation after regular use.
 - Use of benzodiazepines with a longer half-life.
 - Use of higher benzodiazepine doses.
20. Which of the following benzodiazepines is preferred in alcohol withdrawal patients who do not have severe liver disease?
- Alprazolam.
 - Lorazepam.
 - Temazepam.
 - Diazepam.

LEARNER RECORDS: SAMPLE

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A Competence B Performance C Outcome D No Change

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

- | | A | B | C | D |
|---|-----------------------|-----------------------|-----------------------|-----------------------|
| 1. Manage patients at the end-of-life in ways consistent with their stated preferences and appropriately manage patients in hospice | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 2. Evaluate patients in pain and develop a comprehensive treatment plan. | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 3. Utilize both non-pharmacological and pharmacological treatment modalities to manage pain. | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 4. Identify addiction disorders and develop patient-specific treatment options. | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 5. Please identify a specific change, if any, you will make in your practice related to pain, addiction and end-of-life care. | | | | |

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

OVERALL PROGRAM:

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|---|-----------------------|-----------------------|------------------------|
| 7. The program was balanced, objective and scientifically valid | <input type="radio"/> | <input type="radio"/> | _____ |
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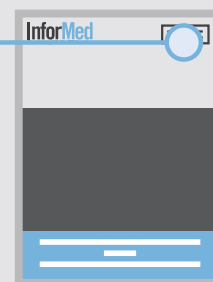
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