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Multimodal Pharmacotherapy for Pain Management

Includes 5 Pharmacotherapeutic/Pharmacology Hours

Audience
This course is designed for nurses involved in the care of patients with pain.

Course Objective
The purpose of this course is to provide healthcare providers with a clear understanding of the concept of multimodal pharmacotherapy for pain relief, including available classes of analgesics.

Learning Objectives
Upon completion of this course, you should be able to:

1. Describe the underlying pathophysiology of pain.
2. Outline the different types of pain.
3. Discuss the mechanism of action and clinical use of opioids in the management of pain.
4. Compare and contrast other analgesic agents that can be used in a multimodal approach to pain management, including nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants, and local anesthetics.
5. Analyze approaches to multimodal pharmacotherapy for pain management.

Faculty
Richard E. Haas, BSN, MSN, EdM, PhD, CRNA, PHRN, LTC US Army Nurse Corps (Retired), is a nurse anesthetist and prehospital registered nurse (instructor) who has published extensively in various areas of healthcare research while providing clinical care in arenas ranging from academic medical centers to austere environments in the third world during both wartime and peacetime. He has a bachelor's degree in nursing from Georgetown University, Master's degrees in education (Boston University) and nursing specializing in anesthesia (State University of New York in Buffalo and U.S. Army), and a PhD from the University of South Carolina. He is a retired lieutenant colonel in the U.S. Army Nurse Corps. He has taught nursing anesthesia, pharmacology, and physiology; mentored students in doctoral programs; and used advanced patient simulation to train students. Dr. Haas has worked in clinical, administrative, education, and research roles. He continues to work as an independent consultant, while taking more time to enjoy life with his wife of 45 years and their children and grandchildren.

Faculty Disclosure
Contributing faculty, Richard E. Haas, BSN, MSN, EdM, PhD, CRNA, PHRN, LTC US Army Nurse Corps (Retired), has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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INTRODUCTION

Pain is one of the most potent safeguards to homeostasis. Experiencing pain allows humans to learn which activities or substances might cause irreparable damage to the body, and thus avoid engaging in those activities or ingesting those substances. However, this system is not perfect. Techniques to ameliorate pain have been actively sought since the earliest recorded history of science and medicine. Opioids, alcohol, mandrakes, and cannabis have all been used through the years in an attempt to mitigate pain [1].

From the 1860s until the 1950s, morphine was the pre-eminent opioid used for the control of pain. It was easily produced, especially as the pharmacotherapeutic industry became increasingly more refined and developed. In the 1950s, researcher Paul Janssen began his work on the synthesis of a new opioid called fentanyl [2]. In 1960, fentanyl was synthesized, and its use became widespread as a result of its safety and efficacy. Two derivatives of fentanyl followed in the 1970s: alfentanil (with a more rapid offset) and sufentanil (with increased potency) [2]. Opioids continue to be the mainstay of severe pain relief.

Even as researchers have lauded the effects of opioids for pain relief, they decried the problems with the use of opioids, particularly the risks of abuse and addiction. In the decade following their widespread use in the Civil War, physicians began to refer to opioid use disorder as the "soldier's disease" [3]. Unfortunately, knowledge of the problem has not led to an immediate solution. Problems with opioid abuse, including use disorder and diversion for illicit use, continue. At the same time, opioids (including fentanyl and its congeners) are widely used for the control of severe pain. There is evidence that even appropriate use of opioids may lead to use disorders and diversion in a subset of patients [4].

In an effort to decrease the use of opioids, it is vital for clinicians to first consider other agents to control pain. Combining various classes of drugs, in lower doses, can help control pain while decreasing side effects. One large dose of an opioid may be effective, but the preferred approach may be to use less or no opioid and to combine other agents, including anti-inflammatories, local anesthetics, alpha-2 receptor agonists, and others, to attain pain relief without the risks associated with opioids. This course will focus on the science behind multimodal pharmacologic pain management and its efficacy.

THE PHYSIOLOGY OF PAIN

Management of pain is a highly complex and patient-centered specialty. Clear understanding of the underlying anatomy and physiology is required to make the correct selection of pharmacologic interventions.

The human body has a number of specialized receptors in the skin, viscera, and periosteum of the bones that send impulses to the spinal cord and brain reporting the presence of pain (***Table 1***) [5]. Of particular interest to those treating pain is the free nerve ending (FNE) (***Figure 1***). There are several types of these unmyelinated nerve endings, and the ones most related to pain and tissue damage information processing are type IVa [6]. FNEs can send an impulse in the form of an action potential into the pain pathways as the result of tissue damage (secondary to trauma or heat) or tissue deformity (severe pressure resulting in tissue destruction). It is helpful to briefly review the concept of the action potential before moving on to an examination of the FNE.

ACTION POTENTIAL

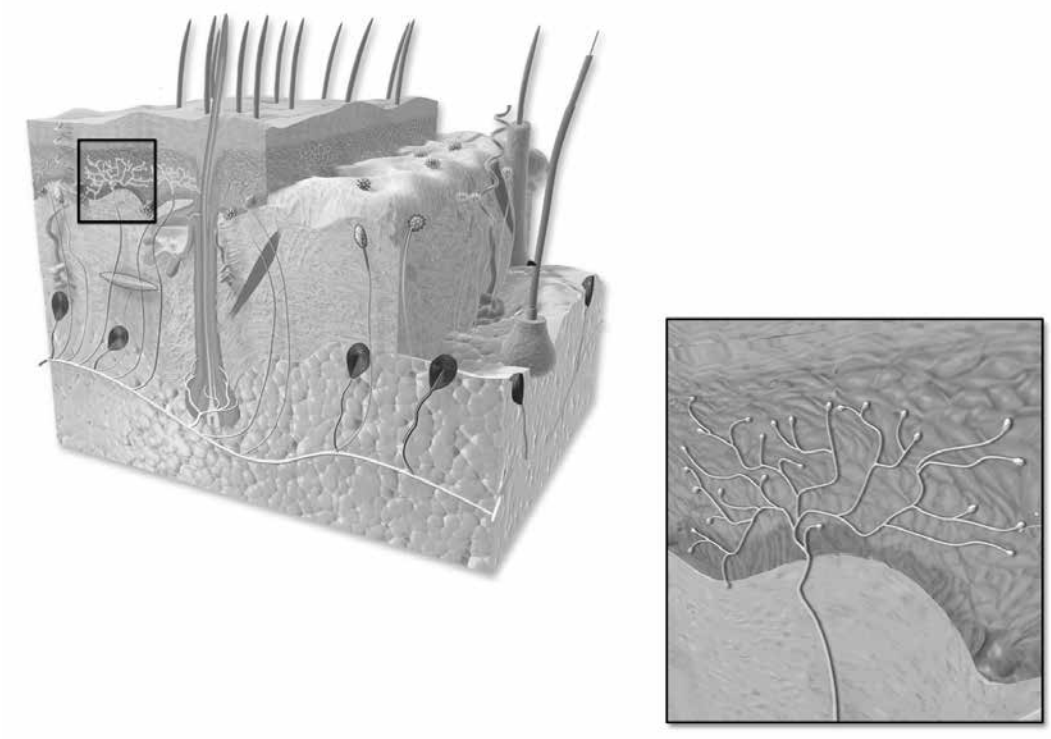
Action potentials are changes in polarity along a nerve based on ion flow into and out of the nerve cell. As the action potential travels down the length of the cell, it will end at a point in the nervous system that results in some form of output, either physical (muscle movement) or experiential (pain). ***Figure 2*** shows some of the details of an action potential and provides and extended explanation of their formation. Of particular importance is the quantity of ions moving at any specific time. The primary ions moving after stimulation and reaching threshold are Na^+ (sodium, into the cell), K^+ (potassium, out of the cell), and Cl^- (chloride, into the cell). After the nerve has fired, the sodium/potassium adenosine triphosphate (ATP)-ase pump works to move sodium out of the cell and potassium back into the cell. A pump is needed because the ions are moving against their gradients, and energy is required in the form of ATP to power the pump.

A variable but set amount of nervous action potential impulses is required to reach threshold. The nerve must receive a sufficient number of input signals (or stimuli) to move its membrane potential above threshold and fire an impulse, sending, in this case, a message of pain along a nerve pathway. Understanding the science behind the action potential and its formation is crucial for the healthcare provider, as many analgesic drugs work by altering the transmissibility of signals sent along the nerve. If the action potential formed in the FNE can be blocked or altered, painful sensations can be mitigated or eliminated.

TYPES OF SENSORY RECEPTORS		
Type	**Function**	**Location**
Free nerve ending	Transmit pain and temperature	Skin, periosteum, arterial walls, joint surfaces
Pacinian (lamellar) corpuscle	Pressure	Skin
Meissner (tactile) corpuscle	Touch	Skin
Muscle spindle	Stretch and pressure	Skeletal muscle
Golgi tendon apparatus	Stretch and pressure	Tendons
Kinesthetic receptor	Three-dimensional location (proprioception)	Joints

Source: Compiled by Author *Table 1*

FREE NERVE ENDING



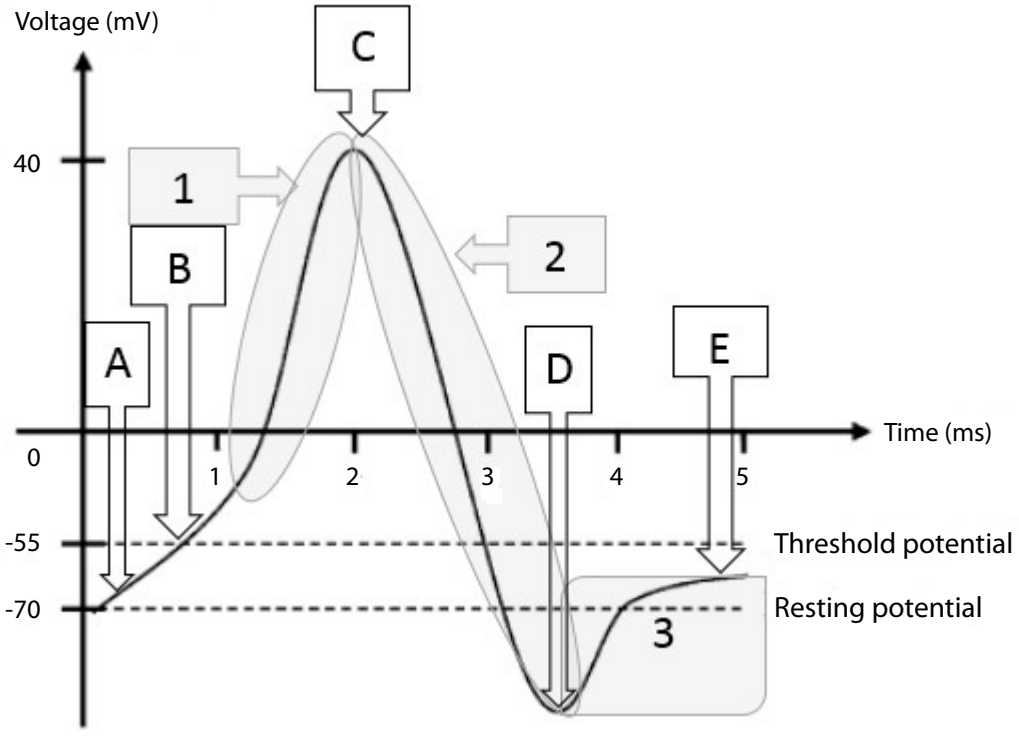
Source: Reprinted from Blausen.com staff (2014). Medical gallery of Blausen Medical 2014. WikiJournal of Medicine 1 (2). *Figure 1*

FREE NERVE ENDINGS AND FIBER TYPES

What are the two primary types of nerves that carry pain data elicited by stimulation of an FNE?

The FNEs are one of the sets of tissue receptors that can be stimulated to send impulses (action potentials) along the length of the nerve for further interpretation either in the spinal cord or various sections of the brain. Despite the study of FNEs over the past decade, the exact mechanism of action is still unknown. There are several postulations about how stimuli cause the firing of FNEs, initiating action potentials and resulting in the experience of pain. FNEs are also referred to as nociceptors. While nociceptors are often described as pain receptors, the purpose of the nociceptor is to alert the body to the presence of tissue damage [8]. FNEs are small structures, with a thin layer of Schwann cells surrounding them. They are branched in appearance and have small varicosities containing mitochondria, vesicles, and an axonal reticulum (analogous

ION MOVEMENT IN ACTION POTENTIAL FORMATION



Point A above shows the resting membrane potential of the nerve. At rest, a certain degree of leakage of both the sodium (Na+) into the cell and potassium (K+) out of the cell occurs. When a painful stimulus is experienced in the periphery, impulses will arrive at some point along a secondary nerve. Note the gradual upslope of the potential within the cell (the section between points A and B). In this example, painful impulses are coming into a section of nerve tissue from a free nerve ending, resulting in opening voltage-gated Na+ channels, resulting in an influx of Na+ that is faster than the outward leakage of K+, leading to an increasing membrane potential. Once membrane potential reaches threshold (point B), a large number of voltage-gated Na+ channels open, resulting in a large shift of Na+ ions from the extracellular fluid to the intracellular fluid, causing the initiation of an action potential (shaded area 1). Voltage-gated K+ and chloride (Cl-) channels then open, allowing K+ efflux and Cl- influx, dropping membrane potential (shaded area 2). The movement of K+ and Cl- is so great that an overshoot occurs, and the nerve hyperpolarizes (or falls below resting membrane potential, point D and shaded area 3). The Na+/K+ ATP-ase pump begins to work (shaded area 3) and equalizes Na+ and K+ gradients to result in a return to normal resting membrane potential.

Source: [7] *Figure 2*

to the sarcoplasmic reticulum or endoplasmic reticulum in other cell types) [5; 9]. The vesicles contain numerous neuropeptides, including substance P and calcitonin gene-related peptide (CGRP), both of which are crucial in spreading action potentials during conditions of tissue destruction resulting in pain [9]. ***Figure 2*** illustrates varicosities in the distal ends of the FNE, but these structures are present throughout the FNEs until they reach larger nerves.

There are two primary types of nerves that carry pain data elicited by stimulation of an FNE: type Aδ or myelinated (fast) nerve fibers and type C or unmyelinated (slow) nerve fibers [5; 8]. Myelinated fibers are insulated with Schwann cells, but with gaps (nodes of Ranvier) in which the nerve fiber is exposed to the environment of the extracellular fluid. The myelinated fibers are also referred to as fast fibers because the action potentials can skip between the nodes of Ranvier in a process called saltatory conduction (rather than traveling the entire length of the axon). Sharp or acute pain, especially from traumatic injury, is usually processed in this fashion.

SIMPLIFIED PAIN PATHWAY

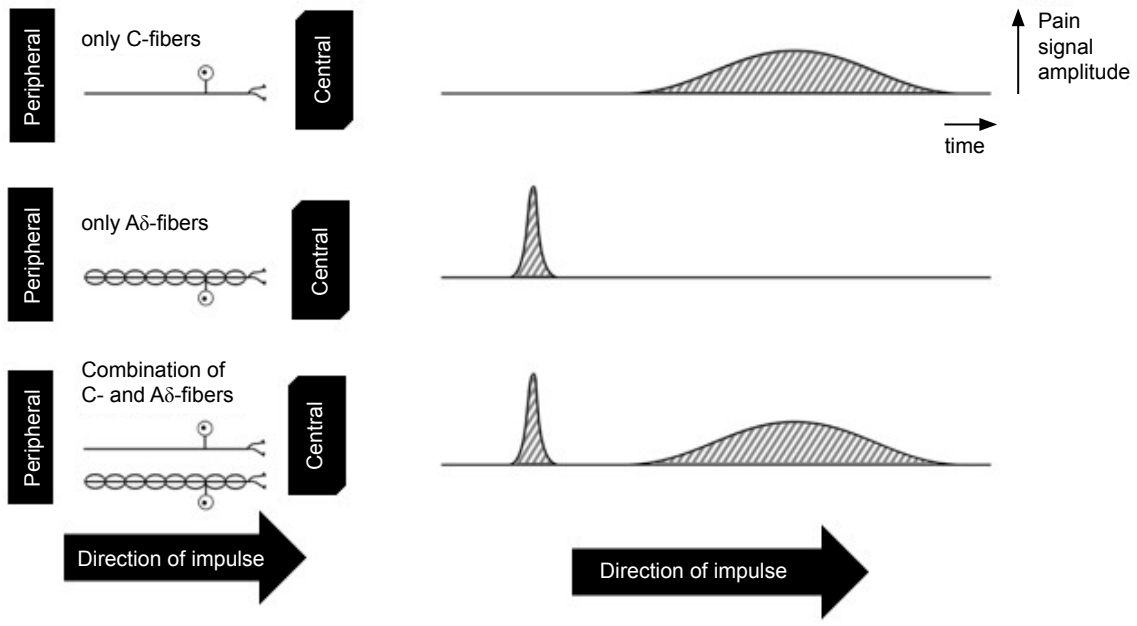


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Figure 3

Type C fibers move impulses more slowly. While myelinated fibers can carry action potential impulses at speeds of 5–30 meters per second, unmyelinated fibers have speeds of 0.4–1.4 meters per second [8]. Most individuals have experienced this type of pain differential speed in their own lives: an acute accidental injury such as cutting one's finger while cooking results in an immediate response followed by an aching sensation. This is because both type A and type C nerve fibers travel in bundles together, and the stimulation of one nerve makes the stimulation of a nearby nerve easier. An example of this phenomenon is seen in ***Figure 3***. The solid line represents an unmyelinated nerve (type C), while the line with nodes represents a myelinated nerve (type Aδ). If the nerves travel together from the site of injury, the patient experiences two waves of pain. Myelinated fibers carrying information about pain tend to be highly localized, dependent on the density of FNEs in the area of injury. Unmyelinated fibers tend to carry information related to aching or less acute or localized pain. A significant amount of visceral pain tends to be carried by unmyelinated fibers, making diagnoses of this type of pain difficult.

PAIN PATHWAYS: GETTING THE INFORMATION FROM THE SITE OF PAIN TO THE CENTRAL NERVOUS SYSTEM

Pain pathways are complex routes over which action potentials are sent from the peripheral nerves to the central nervous system (CNS). An interruption of the pathway at any point tends to mitigate the degree of pain felt by the patient and, in some cases, may alleviate pain entirely. This can be accomplished by blocking some part of the pathway with a local anesthetic or by administering an agent(s) that drives the resting membrane potentials of neurons in a more negative fashion or interrupts the pathway within the brain. One of the key aspects of multimodal pharmacologic pain relief is to use smaller doses of various agents that work at different points along the pathway, minimizing adverse side effects while maximizing the number of sites of action.

Pain and other impulses originate in the peripheral nervous system (PNS), enter the dorsal horn of the vertebra, and then ascend to the brain along the spinothalamic tract. This is a three-neuron pathway containing first-, second-, and third-order neurons. In ***Figure 4***, the spinothalamic tract can be traced from the primary afferent nerve (receiving the pain signals at the site of injury) to the spinal cord, entering via the dorsal

FAST VS. SLOW PAIN TRANSMISSION

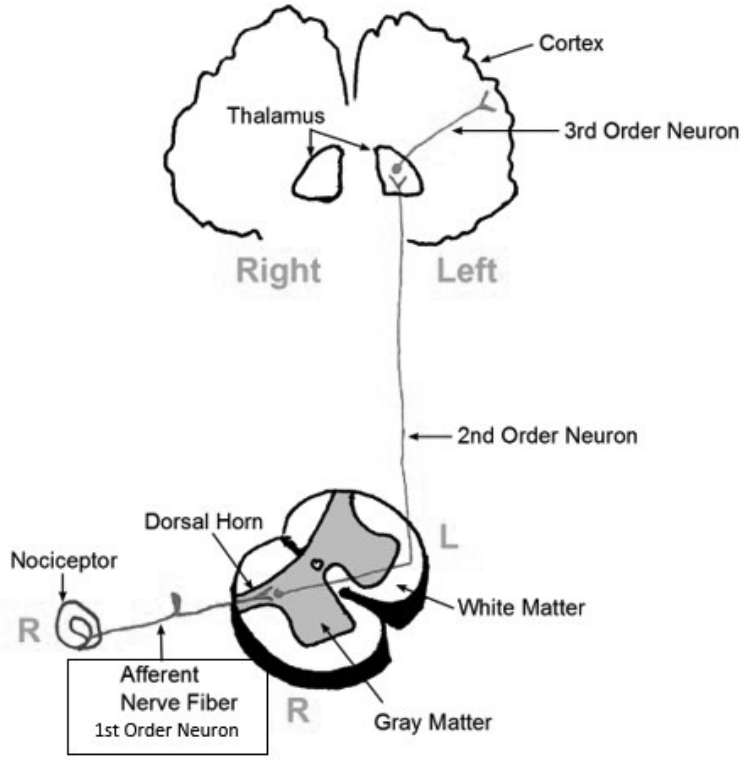

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Figure 4

root of the cord. At this point, the first-order neuron synapses with a second-order neuron. Upon entry into the cord, the second-order neuron crosses from the right to the left (or left to right, if it enters the left dorsal root). This is referred to as decussation. The second-order neuron then rises up the cord in either the anterior or later spinothalamic tract, synapsing with a third-order neuron in the thalamus. This neuron leads to the sensory cortex in the brain, which in turn interprets the exact location and degree of pain.

Local Changes and Injured Tissue

Because pain is adaptive in nature, it is important that signals are sent to the central nervous system to ensure the body responds to maintain homeostasis. As discussed, FNEs exposed to noxious stimuli send action potentials down a specific pain receptor pathway to insure its arrival in the central nervous system [9; 10; 11; 12]. Recall also that action potential generation is dependent upon the release of neurotransmitters, which in turn raise the nerve's membrane potential above threshold. While many neurotransmitters do this, a significant number function to lower resting membrane potential. This environment, in the presence of injury, has been referred to as "inflammatory soup," as a representation of the numerous and diverse substances involved in responses to pain [7]. ***Table 2*** provides a synopsis of most of these substances, focusing on those with the greatest impact in pain management. For nearly every substance, there is some form of pharmacologic antagonist available or in development to nullify its excitatory effect. While ***Table 2*** provides a brief glimpse at how neurons can be excited by local peptides and neurotransmitters, the actual mechanisms by which these changes are made are incredibly complex.

There is a large number of receptors on the neuron's cell membrane, most of which can bind with a specific molecular neurotransmitter. Nearly every drug administered in multimodal pain therapy interacts with one or more of these receptors.

SUBSTANCES AFFECTING THE TRANSMISSION OF IMPULSES IN FREE NERVE ENDINGS AND SOMATIC NERVES	
Substance	**Description**
Bradykinin	Bradykinin is a vasodilator that increases capillary permeability, increases migration of white blood cells, and increases free radicals in inflamed tissue and significantly excites pain receptors.
Calcitonin gene-related peptide (CGRP)	Stimulation of the free nerve endings results in the release of CGRP from the neuron, sensitizing it to stimuli and making the neuron hyperactive.
Norepinephrine	Pain stimulates the sympathetic nervous system, leading to the release of norepinephrine, which has an excitatory effect on the neuron.
Glutamate	Glutamate is an endogenous and highly excitatory neurotransmitter that binds at both the NMDA and AMPA receptors to excite the neuron and facilitate pain transmission.
Histamine	A ubiquitous substance throughout the body, histamine is released by mast cells and binds with excitatory receptors on the neurons and other cells.
Tachykinin	Tachykinins are a broad family of neuropeptides, including substance P, neurokinin A, and neurokinin B, released in response to pain or inflammation. They bind with neurokinin receptors, resulting in increasing excitatory stimulation of the neuron.
Serotonin (5-HT)	During inflammation, 5-HT is released from platelets in the area of injury. In turn, these bind with 5-HT2A and 5-HT3 receptors, resulting in excitation of the nerve.
Prostaglandin	One of the most crucial substances in pain management, prostaglandin sensitizes all aspects of excitatory phenomena in neurons. They are produced from the cell's arachidonic acid supply via the cyclo-oxygenase and lipoxygenase pathways.
Cytokine	Cytokines increase synaptic excitatory transmission in neurons and are represented by such substances as TNF and interleukins (e.g., IL-1b, IL-6).
AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, NMDA = *N*-methyl-D-aspartate, TNF = tumor necrosis factor.	
Source: [5; 10; 11; 12; 13; 14; 15]	*Table 2*

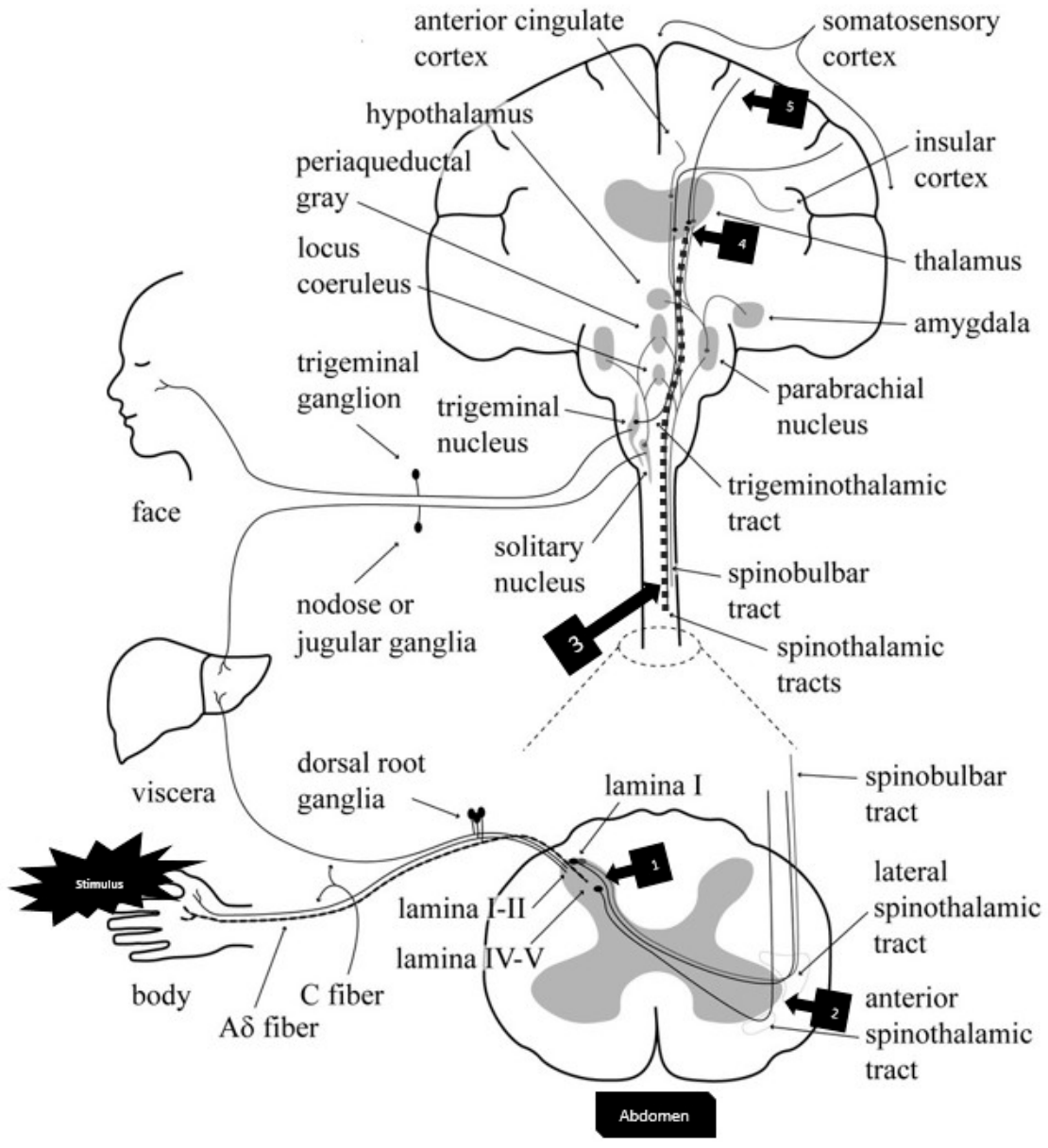
Complex Ascending Pain Pathways

Figure 5 is a complex diagram of the ascending pain pathways. Starting in the lower left corner (with the stimulus), the pain pathway can be seen tracking along both Aδ and C fibers and entering the dorsal root of the spinal cord. The peripheral nerve synapses with a second-order nerve (Box 1) that decussates across the spinal cord; activating or inhibiting the interneurons in the lamina of the dorsal root can stop the impulse from propagating. The pain pathway then begins to ascend the anterior and lateral spinothalamic tracts toward the brain (Box 2). In the neck area of the diagram, the spinothalamic tract has been highlighted (Box 3), and it continues to ascend into the thalamus in the brain. The second-order neurons synapse in a special area of the thalamus called the ventrobasal complex (Box 4) [5]. The thalamus, when activated, is thought to cause the conscious perception of pain and provides an anatomic location for the cell bodies of the third-order neurons [5]. The third-order neurons then ascend to the somatosensory cortex, allowing the patient to localize and quantify the painful stimulus (Box 5).

The thalamus also has neuronal branches that help to stimulate the reticular activating system, the portion of the brain responsible for sleep and waking [5]. The thalamus has numerous projections into other areas of the brain, including the prefrontal cortex and the amygdala, the latter of which is part of the limbic system [16; 17]. The projections of the neurons into the limbic system account for the suffering aspect of pain, where the sensation is overlaid with an emotional experience. As pain is important in preventing homeostasis damage, including an emotional response to pain (in addition to a sensory response) helps ensure the person experiencing pain will avoid the stimulus that led to the pain.

The hippocampus is another area that receives neuronal impulses during painful stimuli [17]. Previous studies have linked decreases in hippocampal volume to major depression; however, the hippocampus also helps process and modify nociceptive stimulation [18; 19]. Further, the hippocampus is the primary site for implanting memories [17].

ASCENDING PAIN PATHWAYS



This is a cross-sectional view looking from the top of the head down toward the feet. As indicated by the box labeled abdomen, the patient is lying face down.

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Figure 5

Patients who are exposed to chronic pain or chronic stress may develop severe pain syndromes refractory to usual treatment. These pain syndromes have been associated with increased production of tumor necrosis factor-alpha (TNFα), a proinflammatory cytokine that sensitizes the patient to increased levels of pain secondary to local inflammation [19]. These inflammatory processes also atrophy the hippocampus, which has been associated with major depressive disorder [20]. It is not unusual, therefore, for unremitted or inadequately treated pain to co-occur with severe depressive disorders [21; 22].

Wide-Dynamic-Range (WDR) Neurons

At this point, it is appropriate to discuss the case of the wide-dynamic-range (WDR) neuron, a self-stimulating type of interneuron. As discussed, interneurons are found in the dorsal horn of the spinal cord and may act to facilitate or inhibit the transmission of nerve impulses, depending upon the receptors and neurotransmitters present. WDR neurons are associated with chronic pain states and are triggered by glutamate and glycine (excitatory neurotransmitters), which in turn activate *N*-methyl-d-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate receptors [5; 12; 23; 24]. The NMDA receptor is a channel between the extracellular fluid and intracellular fluid embedded in the cell membrane. The dorsal horn of the spine has many glutamate- and glycine-releasing interneurons, and in an excitatory state, large numbers of glutamate and glycine neurotransmitters are released from neurons [25]. They have binding sites on NMDA receptors, which allows the movement of both Na+ and Ca2+ into cells, while a comparatively small amount of K+ exits [23; 25]. The NMDA receptor cannot open, even in the presence of glutamate and glycine, without first having the magnesium ion (Mg2+) blocker removed from the center of the channel. The interneurons containing the NMDA receptors, however, have other receptors, allowing them to become excited and fire an impulse. When the initial depolarization occurs, the Mg2+ obstruction is removed from the channel, and the rich environment of glycine and glutamate allows the membrane to continually depolarize. This increases the excitability of the second-order neuron, facilitating the passage of painful stimuli to the brain. As the nervous tissue becomes increasingly excited, further releases of glutamate and glycine occur, prompting more NMDA receptor opening in a positive feedback loop. This is called a windup phenomenon [26]. In other words, the area of injury becomes so excited that hyperalgesia sets in, and, in this state, even the smallest stimulus may result in severe pain. Wind-up phenomena result in a continual stimulation of neurons within the cord, with information processed there being sent to the brain. This is referred to as long-term potentiation and is quite difficult to treat [23; 24].

Knowledge of these pain pathways is necessary to achieve a sense of the many sites in the central and peripheral nervous systems where pain can be treated. As specific drug classes are described, one may return to these sections for a better these diagrams to understand how and where they act in the body.

TYPES OF PAIN

ACUTE PAIN

Pain pathways stimulate many areas of the brain. The brain responds by the release of many neurotransmitters and other hormones to provide a systemic response [10]. As discussed, pain impulses activate the amygdala, which triggers a sympathetic nervous system response, sometimes referred to as the "fight-or-flight" response. The release of norepinephrine and epinephrine results in, among other things, tachycardia, hypertension, and elevated blood glucose levels. Additionally, the local response to the stimulus produces the release of local neurotransmitters, such as substance P, glutamate, CGRP, and brain-derived neurotrophic factor (BDNF) [10; 11]. Of perhaps greater concern is the release of cytokines, which results in a profound inflammatory response. The inflammatory response is usually highlighted by hyperalgesia (exaggerated painful response to a painful stimulus) and allodynia (painful response from a non-pain-inducing stimulus). Take the example of a minor sunburn. If the skin is reddened and inflamed, a pat on the back becomes inordinately painful (hyperalgesia) and simply wearing a shirt may be intolerable (allodynia). In addition to these responses, untreated acute pain may lead to the expression of additional FNEs and nociceptors.

Acute pain usually has an easily recognized proximate cause and can be well-localized. The possible exception is intra-abdominal or pelvic pain, in which unmyelinated nerves are responsible for most nerve impulse propagation. However, even this hard-to-localize pain is often characterized to a general area ("My stomach hurts") rather than being poorly defined ("Everything aches").

In some cases, acute pain is associated with a medical procedure, such as routine surgery. For these patients, it is possible to visualize precisely where tissues have been manipulated and thus the location of the pain. The advantage of treating this form of acute pain is that treatment can be pre-emptive, with the administration of analgesics as part of the overall management plan [27].

CHRONIC PAIN

What is nociceptive pain?

Chronic pain is experienced by nearly one-third of the adult population of the United States and is associated with costs of more than $600 billion per year [11]. It can result in physical and emotional disability. It has become clear that chronic pain is far different from acute pain in its experience and treatment. While acute pain is related to a specific injury site, chronic pain is often centrally mediated and can therefore occur without the stimulation of a peripheral nerve [7; 11;

28]. Unfortunately, while acute pain can serve some adaptive purpose in protecting the person from harm, chronic pain is maladaptive in nature and typically has no beneficial biologic or systemic significance [11].

Historically, the initial approach to diagnosis and management of pain emphasized the identification of disease, lesion, or anatomic site of the pain, without reference to the underlying neural mechanisms or the application of this to treatment considerations [29]. Evidence now strongly supports combining the conventional etiology-based approach with a mechanism-based approach that classifies pain syndromes by the type of maladaptive nervous system alteration that has developed in reaction to the original insult. This approach provides a comprehensive dual therapeutic focus that targets the pathologic sustaining mechanism of the pain as well as the original disease, lesion, or tissue injury that has been the traditional focus of pain management [29; 30]. Such an approach is believed to optimize pain diagnosis and treatment by avoiding the limitations associated with the traditional etiology-based approach [31; 32; 33; 34; 35; 36].

Most pain syndromes involve multiple, often overlapping, neurobiologic mechanisms determined by the stage of the disease process. Current concepts of pain classify these into four main categories: nociceptive, inflammatory, neuropathic, and centralized [37].

Nociceptive pain is a physiologic response to tissue injury, the perception that arises from intense stimulation of specialized peripheral sensory neurons (nociceptors) that respond only to noxious (pain) stimuli. Nociceptive pain is subgrouped by location of involved tissues into somatic pain (muscle or connective tissue) and visceral pain (visceral structures) [38]. Nociceptive pain is considered adaptive during tissue healing but maladaptive and pathologic when it persists after healing has occurred.

Inflammatory pain occurs in response to tissue injury or infection that activates peripheral nociceptors and initiates the immune response. While the resultant production and recruitment of pro-inflammatory mediators to the injury site may serve to perpetuate discomfort, it also facilitates tissue repair; thus, this is considered an adaptive pain mechanism.

Neuropathic pain originates from peripheral or central nervous system injury. Unlike nociceptive and inflammatory pain, the mechanism of neuropathic pain has no adaptive function and is strictly pathologic [32; 39]. Acute pain from somatosensory damage is termed "acute neural injury." The term "neuropathic pain" implies pain that persists beyond the period of expected or actual tissue healing, and the underlying mechanism involves a maladaptive alteration in somatosensory nervous system function [35].

Centralized pain results from heightened nociceptive sensitivity in the absence of detectable peripheral stimulus and with negligible peripheral inflammatory pathology. The mechanism is poorly understood and is regarded as strictly pathologic as it lacks any evident adaptive function. Centralized pain disorders include conditions such as fibromyalgia, tension headache, and irritable bowel syndrome [32; 38; 40].

The persistence of acute nociceptive, inflammatory, or neural injury pain beyond tissue healing or repair reflects ongoing nociceptive activity that has become dissociated from peripheral nociceptive input to become maladaptive. Regardless of whether acute pain originates from tissue injury, tissue infection, or peripheral nerve injury, a similar process occurs by which nociceptive, inflammatory, and neuropathic pain signals are relayed from tissue injury site to the brain. This highly intense or prolonged pain signaling can lead to profound alteration in neuronal pathways that are further "upstream" from the peripheral tissue pain origin. Among these are increased ascending pathway signaling to the brain, reduced descending inhibitory signaling, expansion of pain receptive field, and induction of spontaneous and widespread pain. The resulting peripheral and central pathway hypersensitivity represents a state of abnormal nervous system function, amplified central nervous system sensory signaling, and abnormally low threshold pain response. The pain is no longer a symptom of peripheral insult, but a disease state of the nervous system [35]. This transition from acute to chronic pain occurs in discrete pathophysiologic steps involving multiple signaling pathways [41].

ANALGESIC AGENTS EMPLOYED IN MULTIMODAL PAIN MANAGEMENT

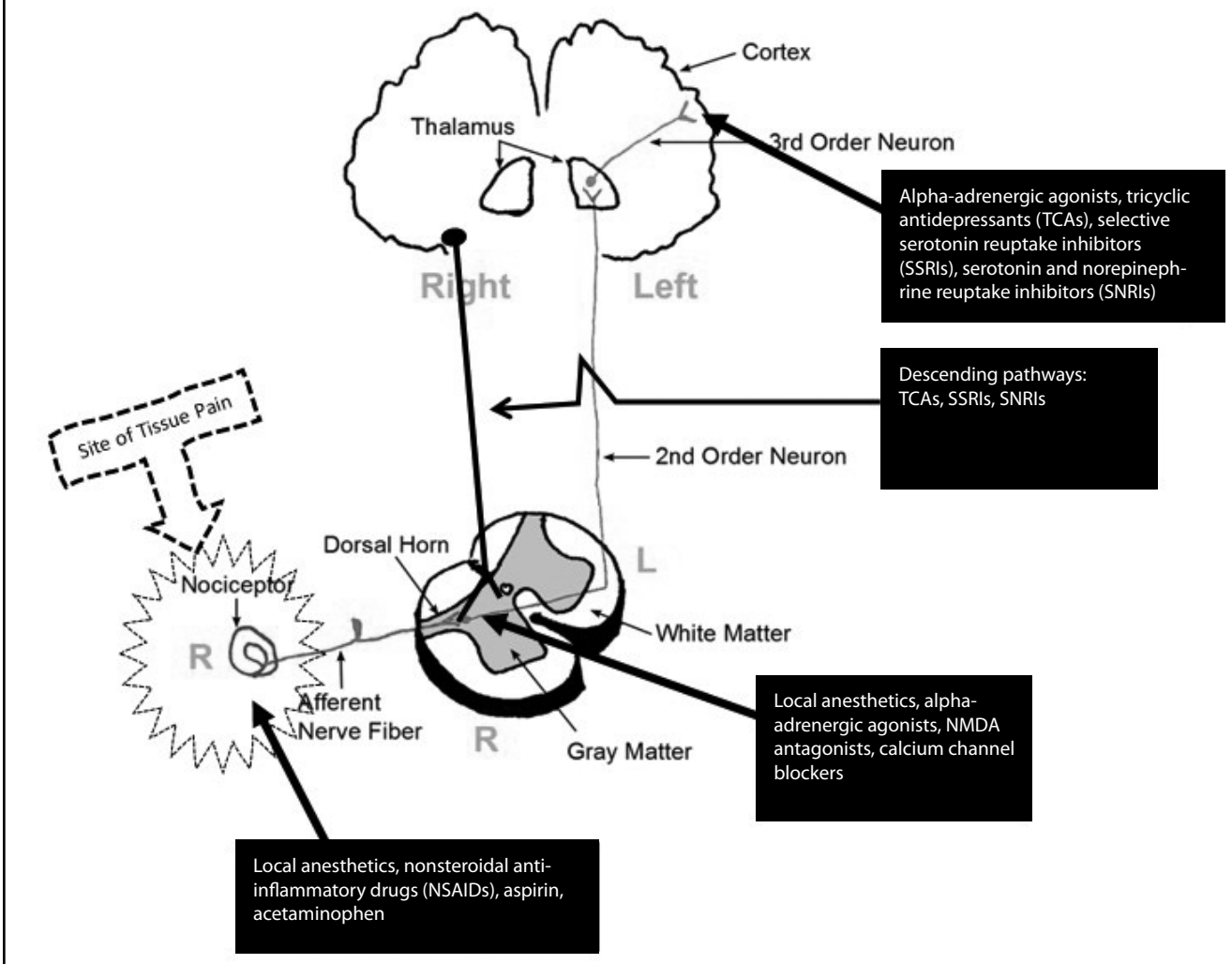
Figure 6 illustrates some of the sites and agents useful in the management of pain. Note that some agents act at more than one site along the pain pathway, and some of the agents enhance the utility of the endogenous descending pain pathways.

OPIOIDS

What are the three primary opioid receptor types?

Opioid analgesics produce therapeutic and side effects by mimicking endogenous opioid activity, although some opioids produce analgesia by activity outside the opioid receptor complex. Opioids widely differ in levels of affinity and activation of opioid receptor subtypes. In addition, inter-individual variation in analgesic response and side effects is significant, largely driven by genetic factors [42]. The complex interaction between unique opioid properties and individual patient characteristics dictates that a patient-tailored approach is required for opioid selection, dose initiation, and titration to optimize safety, analgesia, and tolerability.

SITES AND AGENTS FOR MULTIMODAL ANALGESIA



Source: Bettina Guebeli, licensed under a Creative Commons Attribution-Share Alike 4.0 International license. Modified by author.

Figure 6

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the Institute for Clinical Systems Improvement, there needs to be shared decision-making with the patient about reducing or eliminating opioids to avoid unnecessary complications from long-term opioid use. This involves following and re-evaluating the patient closely, with dose reduction or discontinuation as needed.

(https://www.icsi.org/wp-content/uploads/2020/01/PalliativeCare_6th-Ed_2020_v2.pdf. Last accessed October 20, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

Naturally occurring opioid compounds are produced in plants (e.g., opium, morphine) and in the body (the endogenous opioids) [43]. Endogenous opioids are peptides that bind opioid receptors, function as neurotransmitters, and help regulate analgesia, hormone secretion, thermoregulation, and cardiovascular function. The three primary endogenous opioid peptide families are the endorphins, enkephalins, and dynorphins, and the three primary opioid receptor types are mu, kappa, and delta [44; 45]. A quick overview of this complex pain modulation system is helpful in understanding how opioid analgesics work.

Endogenous Opioid Peptides

Endogenous opioid peptides are neurotransmitter molecules in the opioid receptor complex that produce specific physiologic effects determined by neuronal distributions of the activated opioid receptor type [46]. The endogenous opioid peptides are cleaved from the pro-hormone precursors proenkephalin, pro-opiomelanocortin, and prodynorphin. The endogenous delta opioid receptor peptides are met-enkephalin and leu-enkephalin, cleaved from proenkephalin. Prodynorphin gives rise to kappa opioid receptor agonists dynorphin A and B. Pro-opiomelanocortin encodes the peptide beta-endorphin, which has agonist activity at all three classical opioid receptors. Some endogenous opioid ligands lack specificity for opioid receptor subtypes, such as b-endorphin and the enkephalins [47; 48].

Endorphins

Endorphins are synthesized in the hypothalamus and the pituitary gland. Pain, strenuous exercise, excitement, and orgasm stimulate their release, binding, and activation. Endorphins are popularized as the "natural pain killers" from their ability to induce analgesia and a general feeling of well-being. They are thought to largely mediate analgesia from acupuncture, massage, hydrotherapy, and transcutaneous electrical nerve stimulation therapy [49].

Dynorphins

Dynorphin peptides are synthesized from the precursor pro-dynorphin and have primary affinity and binding at the kappa opioid receptor. Dynorphins are distributed throughout the CNS, with highest concentrations in the brain stem, hypothalamus, and spinal cord. Their physiologic actions are diverse, and their primary function is the modulation of pain response, appetite and weight, circadian rhythm, and body temperature. Dynorphins are linked to stress-induced depression and drug-seeking behavior, and drugs that inhibit dynorphin release are under evaluation for possible use in the treatment of depression related to drug addiction [49].

Enkephalins

Enkephalin peptides, derived from pro-enkephalin, are located throughout the brain and spinal cord and are involved in regulating nociception. Enkephalins inhibit neurotransmission in pain perception pathways, reducing the emotional and physical impact of pain. Enkephalins also reside in the gastrointestinal (GI) tract, where they help regulate pancreatic enzyme secretion and carbohydrate metabolism [49].

Opioid Receptors

Opioid receptors are expressed throughout the CNS and PNS on key nodes within the pain pathway and are highly concentrated in areas involved with integrating pain information [50]. Opioids vary greatly by receptor affinity, binding, and activity and can bind to produce agonist, partial agonist, or antagonist receptor activity [44]. As noted, the analgesic activity and the side effects result from mimicry of endogenous opioids, achieved by the beta-phenylethylamine group moiety shared by endogenous and exogenous opioid receptor ligands that facilitate opioid receptor binding [51].

Mu Opioid Receptors

Mu receptors are the primary mediators of analgesia produced by opioid analgesics in clinical use. Their greatest CNS concentration is in the thalamus, medulla, periaqueductal gray area, neocortex, amygdala, dorsal horn, inferior and superior colliculi, and brain stem [44; 49; 52]. PNS occupancy includes the peripheral sensory neuron dorsal root ganglion, stomach, duodenum, jejunum, ileum, and proximal and distal colon. Mu receptors in non-neural tissue are found in the vascular and cardiac epithelium, keratinocytes, vas deferens, and Sertoli cells [53].

Mu opioid receptors in the amygdala and nucleus accumbens mediate opioid reward response (e.g., euphoria). In this brain region, opioids bind to and activate mu receptors, which inhibit gamma-aminobutyric acid (GABA) to increase dopamine transmission [50]. Mu opioid receptors broadly distributed in the limbic system mediate emotional response to pain and analgesia. In the medial thalamic nuclei, they relay spinothalamic inputs from the spinal cord to the cingulate gyrus and limbic structures [54].

Kappa Opioid Receptors

Kappa opioid receptors bind dynorphin as the primary endogenous ligand. In the CNS, they are highly concentrated in the caudate-putamen, nucleus accumbens, amygdala, brain stem, neural lobe of the pituitary gland, and hypothalamus. In the PNS, these receptors are found in the sensory neuron dorsal root ganglion, stomach, duodenum, jejunum, ileum, and proximal and distal colon. They are primarily found in the limbic system, brain stem, and spinal cord. Their major effects include spinal analgesia, sedation, dyspnea and respiratory depression, dependence, and dysphoria [53]. The kappa opioid receptor subtype k3 is considered the primary analgesic mediator [55].

Delta Opioid Receptors

Delta receptors are mostly confined to CNS structures of the pontine nuclei, amygdala, olfactory bulbs, and deep cortex, but are also found in the GI tract and the lungs. They mediate spinal and supraspinal analgesia and the psychomimetic and dysphoric effects of opioid analgesics [49; 56].

COMMONLY USED OPIOIDS			
Drug	**Functional Category**	**Route(s)**	**Comparison to Morphine[a]**
Morphine	Mu receptor agonist	IM, IV, PO, inhaled vapors	1
Hydromorphone (Dilaudid)	Mu receptor agonist	PO, SQ, IM, IV	10
Fentanyl (Actiq, Sublimaze)	Mu receptor agonist	PO, IV, buccal film, transdermal patch	100
Oxycodone (Roxicodone, OxyContin)	Mu receptor agonist	PO	1.5
Tramadol (Ultram, ConZip)	Mu receptor agonist	PO, IV	0.1
Hydrocodone (Hysingla ER)	Mu receptor agonist	PO	1
Oxymorphone (Numorphan)	Mu receptor agonist	PO, SQ, IM, IV	0.3
Meperidine (Demerol)	Mu receptor agonist	PO, IM, IV	0.1
Methadone (Methadose)	Mu receptor agonist	PO, SQ, IM, IV	Dose dependent
Codeine (Codeine)	Mu receptor agonist	PO	0.17
Buprenorphine (Belbuca, Butrans, Sublocade)	Partial mu receptor agonist	PO, buccal film, transdermal patch, IM, IV	30
Butorphanol (Stadol)	Mixed agonist/antagonist	Nasal spray, IM, IV	2
Nalbuphine (Nubain)	Mixed agonist/antagonist	SQ, IM, IV	1
Sufentanil (Dsuvia)	Mu receptor agonist	IV	1,000
Naloxone (Narcan)	Antagonist	IV, IM, SQ, nasal spray	–
[a]Assuming the pain relief value of morphine is 1, this is the comparative pain relief value of each agent. IM = intramuscular, IV = intravascular, PO = oral, SQ = subcutaneous.			
Source: [57; 58]			*Table 3*

Other Potential Opioid Receptors

Other opioid-like receptors have been identified in the CNS, including the opioid receptor like-1 (ORL-1). In contrast to the classic opioid receptors, the ORL-1 receptor is insensitive to the opioid antagonist naloxone. Opioids can bind to and activate the toll-like receptor 4 (TLR4), an innate immune pattern-recognition receptor [50].

Opioid Analgesic Mechanism

Opioid analgesia results from a complex series of neuronal interactions, largely mediated by the high density of opioid receptors in the dorsal horn of the spinal cord and in subcortical regions of the brain [46]. The analgesic effects of opioids result from two general processes: 1) direct inhibition of ascending transmission of pain signaling from the dorsal horn of the spinal cord, and 2) activation of descending pain control circuits from the midbrain to the dorsal horn of the spinal cord [49]. All three opioid receptor types mediate spinal analgesia. Supraspinal analgesia is primarily mediated by mu opioid receptor subtype 1. Opioid receptors are coupled to the superfamily of inhibitory G proteins. Receptor activation inhibits adenylate cyclase, reducing generation of cyclic adenosine 3,5 monophosphate and other second messengers. Potassium conduction is activated, inhibiting calcium influx to hyperpolarized target cells and reducing their response to depolarizing pulses. Neurotransmitter release is inhibited, and generation of postsynaptic impulses is decreased [46; 50].

Although drugs such as morphine are highly selective for mu opioid receptor and bind multiple mu receptor subtypes, mu opioid agonists greatly differ by interaction with different receptor variants and other opioid and non-opioid receptors [45]. A pharmacologically and clinically relevant classification approach is classifying opioid agents by functional interaction as mu receptor agonists, partial agonists, mixed agonists-antagonists, or antagonists (***Table 3***).

Spinal Level

The spinal cord dorsal horn is a primary analgesic site of opioids and is densely populated with mu (70%), delta (20%), and kappa (10%) opioid receptors. Opioid receptors are localized on presynaptic afferent fibers, interneurons, and postsynaptic projection neurons [50]. Opioids bind to and activate mu receptors, which inhibit the release of pain mediators such as substance P, glutamate, and nitric oxide from nociceptive afferent neurons. Spinal level analgesia appears to elevate pain thresholds [46].

Supraspinal Level

At supraspinal levels, opioids produce analgesia by attenuation of the subjective evaluation of pain. After morphine is given for severe pain, patients report pain but without the associated anguish and distress. Conscious awareness and pain response are retained but modified by changes in emotional response to pain, mediated in part through opioid receptors in the limbic system [46].

Opioid receptors are highly concentrated in the medial thalamus, where incoming sensory information associated with intense and deep pain is filtered and then relayed to the cerebral cortex. This opioid effect on medial thalamus pain signal filtering greatly contributes to analgesia [46].

Opioid receptors are highly localized in subcortical brain regions where descending pain-modulating pathways originate. Normally, these pathways are inhibited by GABAergic neurons that project to descending inhibitory neurons of the brain stem. Opioid analgesics bind to and activate mu receptors on GABAergic neurons; this inhibits GABA to activate descending pain-modulating pathways [46; 50]. In addition, opioids activate ascending serotonin/norepinephrine pathways that project to forebrain centers to regulate the emotional response to pain [44].

The greatest factor that contributes to opioid analgesia is concentration of the drug on the mu receptor, which can be altered by pharmacokinetic processes that influence plasma concentration of the opioid by impacting its absorption, distribution, metabolism, or excretion. Intrinsic properties of the opioid, such as lipid solubility, also contribute to opioid receptor concentration [59].

Neuropathic Pain

Opioid analgesics have historically been considered less effective in neuropathic pain, but more recent evidence provides some support for their use. The extent of neuropathic pain reduction correlates with the duration of opioid therapy, possibly accounting for the mixed results in short-term studies [60; 61]. A 2011 study discovered previously unknown mu and kappa receptor expression on numerous peripheral tissues, immune cells, and joint capsules/synovium. The administration of opioids by injection into painful peripheral tissue sites results in pain relief in the absence of CNS activity, which supports the existence of localized peripheral opioid receptors [62].

Opioid effectiveness in neuropathic pain may be influenced by the capacity to inhibit voltage-gated sodium channels and individual channel type. Buprenorphine is more effective in blocking sodium channels than meperidine, lidocaine, and bupivacaine, possibly from greater lipophilicity, as this is a major factor in local anesthetic potency [61]. Sufentanil, fentanyl, and tramadol, but not morphine, are effective in blocking neuronal Nav 1.2 and may have greater clinical effect in some forms of neuropathic pain [63].

Inflammation enhances opioid anti-nociceptive action by peripheral mechanisms that activate during later (but not early-stage) inflammation, suggesting that timing of opioid administration contributes to analgesic efficacy in inflammatory pain [62]. Opioids are also effective in reducing the "air hunger" of dyspnea in patients suffering from cancer or respiratory or cardiovascular insufficiency [44].

Opioid Antagonists

A fourth group of opioids, opioid antagonists, bind and inactivate opioid receptors. Naltrexone and naloxone have traditionally been used to reverse potentially fatal overdose from opioid receptor agonists such as morphine or heroin. Opioid agonist molecules on mu opioid receptor are displaced, agonist effects on mu opioid receptor are abruptly halted, and opioid-dependent patients rapidly experience full alertness, analgesic loss, and opioid withdrawal [64].

Clinical trials with low-dose naltrexone have found unexpected and paradoxical enhancement rather than blockade of analgesia when co-administered with morphine and other opioid agonists in postoperative pain or severe intractable pain. Other evidence suggests analgesic efficacy as monotherapy in Crohn disease, irritable bowel syndrome, and fibromyalgia [65]. These findings led to the development and introduction of the peripheral-acting mu receptor antagonists alvimopan, methylnaltrexone, and naloxegol for severe opioid-induced constipation [66; 67].

In addition to opioid-induced constipation, opioid antagonists are U.S. Food and Drug Administration (FDA)-approved for the treatment of alcohol and opioid use disorder (naltrexone 50–100 mg/day oral) and opioid overdose (naloxone 0.4–1.0 mg/dose IV or IM). In pain medicine, the dose ranges of naltrexone and naloxone are substantially lower. Of the two, naltrexone is much more widely used, and published pain medicine studies have used dose ranges of 1–5 mg (termed "low-dose") or <1 mg in microgram amounts (termed "ultra-low-dose") [65]. For example, case studies have reported dramatic improvement in refractory pain with intrathecal administration of an opioid agonist combined with ultra-low-dose naloxone in the low nanogram range [68].

COMMONLY USED NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs) AND ACETAMINOPHEN	
Drug	**Route(s)**
Meloxicam (Anjeso)	IV, PO
Ketorolac (Toradol)	PO, IM, IV, eye drops, nasal spray
Ibuprofen (Motrin, Advil)	PO, IV
Diclofenac (Cataflam, Voltaren)	PO, IM, IV, topical gel
Acetaminophen (Tylenol)	PO, IV, rectal
Naproxen (Aleve, Anaprox)	PO
Celecoxib (Celebrex, Elyxyb)	PO
Aspirin	PO
Source: [74; 75]	*Table 4*

The mechanism of low-dose and ultra-low-dose opioid antagonists is not fully known and is the subject of investigation [65]. One explanation describes a sequential action, whereby binding and inhibition first occurs at excitatory receptors, followed by binding at inhibitory receptors. This decrease in excitation facilitates a broader clinical expression of inhibitory function, which potentiates analgesia and reduces adverse effects. For example, with opioid-induced hyperalgesia, ultra-low-dose naltrexone appears to act through excitatory blockade to promote analgesia and tolerability [69; 70].

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

How do NSAIDs alleviate pain?

NSAIDs alleviate pain by inhibiting the conversion of arachidonic acid to prostaglandins catalyzed by COX isozymes. Nonselective NSAIDs inhibit COX-1 and COX-2 and include ibuprofen, aspirin, and naproxen. The nonselective action inhibits the formation of both gastroprotective-mediating prostaglandins and pain-promoting prostaglandins, increasing the risk of serious toxicities such as GI ulceration and bleeding. This prompted the development of selective COX-2 inhibitors, which produce fewer GI side effects but are linked with an increased risk of cardio-renal morbidities [71]. To mitigate risk of GI adverse events, proton pump inhibitors are recommended for use in some patients using NSAIDs [72].

Acetaminophen is available over the counter and is also included in combination with many prescription opioids. Analgesia is achieved through central but not peripheral inhibition of prostaglandin. Although effective in mild pain, acetaminophen is not anti-inflammatory. The side-effect profile is relatively benign with intermittent use at recommended labeled dosing, but long-term or high-dose use can be hepatotoxic, and the daily dose should never exceed 4 g. Acetaminophen is recommended over NSAIDs as an analgesic in patients with GI, renal, or cardiovascular comorbidity [73].

While beneficial in the management of pain, some patients with reactive airway disease may develop bronchospasm, although this adverse effect is rare [5]. In addition, prostaglandins are vasodilators. A constitutive level of circulating prostaglandin is necessary to maintain adequate vasodilation in the afferent limb of the glomerulus to assure renal blood flow in the kidney. Overuse of NSAIDs may result in decreased glomerular blood flow, resulting in decreased elimination of toxins from the body and, in especially severe states, renal failure [5]. The most commonly used NSAIDs are listed in ***Table 4*** [74; 75].

LOCAL ANESTHETICS

Local anesthetics prevent the generation and propagation of nerve impulses in response to painful stimuli. The basic chemical structure of a local anesthetic consists of an aromatic ring (which enhances lipid solubility) and an intermediate ester or an amide chain and a terminal amine [8]. As such, all of these agents are classified as either an ester type or an amide type. The type of anesthetic used and the inclusion of a vasoconstrictor (e.g., epinephrine) will influence the duration of action. Certain factors, such as the presence of active infection in the area to be anesthetized, heightened patient anxiety, or inaccurate deposition of the agent, may affect the ability of a local anesthetic to achieve the appropriate level of anesthesia.

The local anesthetics lidocaine and bupivacaine block Na^+ influx of voltage-gated ion channels in afferent neuron terminals, inhibiting depolarization and generation of action potentials, resulting in the transmission of fewer nociceptive impulses to the spinal cord. In clinical application, topical lidocaine is used for neuropathic pain to block hyperactive sodium ions in damaged peripheral nerves and inhibit transmission of ectopic impulses to the dorsal horn. This action interferes with peripheral and central sensitization and maladaptive neuroplasticity [71; 76].

MAXIMUM DOSES OF LOCAL ANESTHETIC[a]					
Local Anesthetic	**Ester or Amide**	**Maximum Dose Per Kilogram Plain**	**Maximum Dose Plain[b]**	**Maximum Dose Per Kilogram with Epinephrine**	**Maximum Dose with Epinephrine[b]**
Bupivacaine (Marcaine)	Amide	2 mg/kg	175 mg	3 mg/kg	225 mg
Levobupivacaine (Chirocaine)	Amide	2 mg/kg	200 mg	3 mg/kg	225 mg
Lidocaine (Xylocaine)	Amide	5 mg/kg	350 mg	7 mg/kg	500 mg
Mepivacaine (Carbocaine)	Amide	5 mg/kg	350 mg	7 mg/kg	500 mg
Ropivacaine (Naropin)	Amide	3 mg/kg	200 mg	3 mg/kg	500 mg
Prilocaine (Citanest)	Amide	6 mg/kg	400 mg	8 mg/kg	250 mg
Procaine (Novocaine)	Ester	7 mg/kg	1,000 mg	10 mg/kg	600 mg
Tetracaine (Amethocaine)	Ester	0.2 mg/kg	20 mg	N/A	1,000 mg

[a]Doses vary by country and institution, familiarize yourself with your local policies regarding maximum doses before administering
[b]If administering a local anesthetic to a large patient, stop at the maximum dose, even if the mg/kg dose would exceed it.

Source: [82; 83; 84] *Table 5*

Capsaicin defunctionalizes nerve fiber terminals through multiple mechanisms to produce analgesia. The initial reduction in neuronal excitability and responsiveness result from inactivation of voltage-gated sodium channels and direct desensitization of plasma membrane TRPV1 receptors. This is followed by extracellular Ca2+ entry of TRPV1 and release from intracellular stores to overwhelm the TRPV1 receptor intracellular Ca2+ buffering capacity, subsequent activation of calcium-dependent proteases, and cytoskeleton breakdown [77; 78]. The persistent effect involves extracellular Ca2+ entry of TRPV1 and release from intracellular stores to overwhelm TRPV1 receptor intracellular Ca2+ buffering capacity, subsequent activation of calcium-dependent proteases, and cytoskeleton breakdown [77; 78]. Capsaicin is available as a high-potency (8%) patch and as a lower-concentration cream. A single 60-minute application may provide up to 12 weeks of analgesia [76]. Capsaicin may initially cause pain because substance P is released from nociceptive terminals to initiate nociceptive firing. The analgesic response follows as nociceptive terminals desensitize to elevate pain threshold [79].

The use of local anesthesia has become more popular and may be more precisely administered being guided by ultrasonography. Ultrasound technology allows for optimized needle placement, resulting in fewer failed blocks and lower doses. These blocks can be performed before having a procedure performed. When administered before surgery, local anesthetic blocks allow for lower doses of anesthetic agent, along with prolonged postoperative pain relief. In one study, when a local anesthetic block was provided in addition typical analgesic therapy following total knee replacement, morphine doses, pain scores, and nausea were all significantly decreased compared with those who received usual treatment [80].

However, local anesthetics are not without drawbacks, and overdose resulting in local anesthetic systemic toxicity (LAST) is a concern [81]. Because local anesthetics are designed to cross phospholipid membranes, they easily enter the brain and heart, where the blockade of ion channels can have adverse effects. Normally, the first symptoms in patients who are conscious are a metallic taste and/or ringing in their ears (tinnitus). If left untreated, this can progress to excitatory symptoms, followed by drowsiness, coma, and even death [81; 82]. ***Table 5*** provides key information about commonly used local anesthetics, including maximum doses.

The closer to the vasculature the site of injection is, the more likely that the local anesthetic will undergo rapid vascular uptake and result in adverse effects. Mixing the agent with epinephrine, a vasoconstrictor, decreases uptake, thus prolonging the anesthetic effect and decreasing the likelihood of complications. As this is the case, it is possible to give more local anesthetic when it is mixed with epinephrine [82; 83; 84].

In the event of an accidental overdose, there is a specific protocol for treatment [81; 82]. As soon as LAST is detected, the patient should be administered an IV bolus injection of 20% lipid emulsion 1.5 mL/kg^{-1} over one minute. An infusion of 20% lipid emulsion should be started at a dose of 15 mL/kg^{-1}/hour. If after five minutes cardiovascular stability is not restored or the patient further deteriorates, a maximum of two repeat boluses may be administered, with five minutes between injections. At the same time, the infusion rate may be doubled. The infusion should continue until the patient has stabilized or the maximum dose of emulsion (12 mL/kg^{-1}) has been given. The use of lipids to rescue these patients is a relatively new development, so review is important for those in clinical areas with high use of local anesthetics [85].

CALCIUM CHANNEL BLOCKERS

The gabapentinoids, gabapentin and pregabalin, are widely used in the management of both postoperative and chronic pain relief. Their names may give the impression they interact with gamma-amino butyric acid (GABA), but this is not the case [86; 87]. Gabapentin and pregabalin are anticonvulsants that are also effective in a wide range of neuropathic pain conditions. Their mechanism of action involves selective binding to and blockade of the α2δ1 subunit of voltage-gated calcium channel in various brain regions and the superficial dorsal spine. This inhibits the release of glutamate, norepinephrine, and substance P to decrease spinal cord levels of neurotransmitters and neuropeptides [76; 88; 89]. The binding affinity of pregabalin for the calcium channel α2δ1 subunit is six times greater than gabapentin, which is reflected in the greater efficacy of pregabalin at lower doses. Because gabapentin possesses a shorter half-life and nonlinear absorption, pregabalin is easier to titrate and better tolerated [89].

While having a long history in the treatment of chronic pain, the use of these agents to prevent postsurgical pain is relatively new. In one study of 90 women scheduled for abdominal hysterectomy, a control group was compared to groups receiving either 300 mg pregabalin or 900 mg gabapentin administered one to two hours prior to surgery [86]. The average time until first request for analgesia was 31 minutes in the pregabalin group, 16 minutes in the gabapentin group, and 7 minutes in the control group. There was no difference in demographic variables, including length of surgery, across the three groups. In this case, preoperative administration of a gabapentinoid was shown effective in lengthening the duration of analgesia [86].

The locus coeruleus is activated during normal responses to painful stimuli. However, in patients with chronic pain, stimuli inhibit rather than activating the locus coeruleus, dampening analgesic response [90]. When gabapentin is administered to these patients, glutamate is released in the brain, which in turn stimulates the locus coeruleus, restoring its analgesic function [91].

ALPHA-ADRENERGIC AGONISTS

While more commonly associated with the autonomic nervous system and its functions, alpha-adrenergic agonists can also function in the relief of pain, as well as decreasing the sympathetic side effects which accompany pain, including hypertension and tachycardia. Antinociceptive activity of the α-2 adrenoceptor agonists clonidine and tizanidine includes modulating dorsal horn neuron function and norepinephrine and 5-HT release, potentiating mu-opioid receptors, and decreasing neuron excitability through calcium channel modulation [92]. Clonidine is available as a transdermal patch for use in neuropathic pain states. Local use enhances release of endogenous enkephalin-like substances. Intrathecal or epidural administration with opioids and/or local anesthetics is favored in treating neuropathic pain because the synergistic effect improves pain control. Tizanidine is used as a muscle relaxant and antispasticity agent; its use in the management of musculoskeletal pain is off label [76; 79].

Dexmedetomidine was originally approved as a short-term sedative analgesic for mechanically ventilated patients in the intensive care unit [93]. Dexmedetomidine is far more selective as an alpha-adrenergic agonist and has the same central action around the locus coeruleus [93]. As time passed since its introduction, the use of dexmedetomidine has increased, especially among patients with comorbidities (e.g., heart and vascular disease, morbid obesity). Its cardiovascular stability, along with its minimal effect on respiratory drive after the infusion is terminated, have made this agent popular in both the intensive care unit and the operating room. Aside from its use as a sedative or aesthetic agent, use of dexmedetomidine has been explored in patients with refractory end-of-life pain. In a case study, a male patient, 58 years of age, with chronic pancreatitis secondary to alcoholism reported inadequate pain relief despite receiving a combination of oxycodone, nortriptyline, and lorazepam. Increased inpatient intravenous opioids and ketamine still brought the patient no relief, and dexmedetomidine was attempted as a last resort. An infusion of dexmedetomidine brought the patient's pain under greater control, to the extent that he was able to sit in a recliner

and visit with family [94]. Based on this and other reports, dexmedetomidine is being explored as a possible option in palliative care.

Alpha-adrenergic agonists are also found in the area of the brain where projections from the locus coeruleus inhibit an inhibitory portion of the brain responsible for arousal. When alpha-adrenergic agonists act in this area of the brain, they block the ability of the nerves projecting from the locus coeruleus to inhibit the second-order neuron. Thus, these agents, in sufficient doses, render the patient somewhat drowsy [95]. This is important to remember, as the drowsiness associated with the original alpha-adrenergic agonists made their use problematic.

ANESTHETIC DRUGS

Anesthetics are powerful agents typically used in the operating room to reduce the capacity for consciousness and diminish the pain associated with surgery. Two examples are ketamine and nitrous oxide. These agents are quite different; the first is an injectable dissociative anesthetic with variable effects depending on the dose, and the second is an inhaled vapor with profound analgesic effects [18; 96; 97].

Ketamine

Ketamine is a phencyclidine anesthetic given parenterally, neuraxially, nasally, transdermally or orally in subanesthetic doses to alleviate a variety of pain conditions, including severe acute pain, chronic or neuropathic pain, and opioid tolerance [79]. The mechanism of analgesic effect primarily involves NMDA receptor inhibition. Thus, patients with NMDA-mediated central sensitization are likely to realize significant benefit from treatment with ketamine. Ketamine also has activity on nicotinic, muscarinic, and opioid receptors and exerts both anti-nociceptive and anti-hyperalgesic effects, with the latter produced at lower dose ranges [98].

Ketamine is one of very few therapies demonstrating substantial and durable pain reduction of treatment-refractory chronic regional pain syndrome [99]. Potentially distressing adverse reactions (e.g., hallucinations, disturbing dreams, out-of-body experiences) and unwanted changes in mood, perception, and intellectual performance have limited its clinical use in pain control. However, trials have effectively controlled these side effects with high-dose co-administration of midazolam or lorazepam combined with either clonidine or ondansetron [100; 101].

The American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists recommend that subanesthetic ketamine infusions be considered for patients undergoing painful surgery and patients undergoing surgery who are opioid-dependent or opioid-tolerant.

(https://rapm.bmj.com/content/rapm/43/5/456.full.pdf. Last accessed October 20, 2022.)

Strength of Recommendation: B (There is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial.)

Ketamine, however, also has its down sides. One of the most concerning is the formation of psychotomimetic behaviors, and the presence of hallucinatory phenomena after its administration. Fortunately, these are dose dependent in nature and rarely occur at the doses required to treat pain [102; 103]. It has also become a drug of abuse and misuse. Most notoriously, ketamine became known as a "date-rape drug," because it was administered in drinks to unknowing victims who were subsequently sexually assaulted by their predators. Because ketamine causes amnesia, victims have little or no memory of what occurred to them, although they often experienced after-effects, such as pain. As a result of this growing criminal use, Congress passed the Drug-Induced Rape Prevention and Punishment Act of 1996. During this period and the decade following, there was increased awareness of the dangers of ketamine and other drugs that were used in a similar manner, such as flunitrazepam (Rohypnol) and gamma hydroxybutyric acid (GHB) [104]. As a result, ketamine developed a stigma, and this negative view may persist in many minds.

Today, ketamine is increasingly being used to treat patients with treatment-refractory major depressive disorder, which frequently co-occurs in those with chronic pain. The agent appears to actually increase the size and volume of the hippocampus, thus treating the cause of depression [18; 105]. In patients who are imminently suicidal, short-duration doses have been found to significantly reduce suicidal ideation [106].

Nitrous Oxide

Nitrous oxide (chemical formula N_2O) is a component familiar to many, as it is commonly used today to facilitate comfort and address anxiety in dental settings. Historically, it has been used in both dental and medical interventions. Nitrous oxide is a compressed gas and is one of the oldest anesthetic agents in use, with its origins dating back to 1772 [96]. Unlike the inhaled hydrocarbons commonly used as part of a general anesthetic, nitrous oxide has potent analgesic properties. It is thought that nitrous oxide works to enhance the endogenous descending pathways to the alpha-2 and GABA-A neurons in the spinal cord, decreasing the ability of the second-order neurons to depolarize and carry painful stimuli to the brain. When administering nitrous oxide, it is crucial to ensure that oxygen is added to prevent the administration of 100% nitrous oxide to the patient, which would rapidly result in hypoxia and death. All certified nitrous oxide delivery devices have lockout systems to preclude this from happening.

Nitrous oxide is given as a percentage of total inhaled gas flow. The route of administration is inhalation via a mask secured to the patient's nose. For analgesic purposes, the concentration is typically 50% to 70% nitrous oxide with oxygen. Onset of action can occur in as quickly as 30 seconds, with the peak effects seen in five minutes or less. Nitrous oxide diffuses into the alveolus very quickly, accounting for its rapid uptake and circulation to the brain. Nitrous oxide is not metabolized in the body. It is eliminated via respiration within minutes after 100% oxygen is inhaled at the conclusion of the intervention [107].

Repeated doses can be problematic, as extended use of nitrous oxide has been linked to vitamin B12 deficiency [108]. As such, serum vitamin B12 level may need to be measured before and after treatment. Of more concern is the continuous exposure of hospital or clinic staff to chronic low doses of nitrous oxide [96]. Limits of nitrous oxide in the ambient environment are strict and tightly regulated by the by the National Institute for Occupational Safety and Health (NIOSH) [109]. The maximum recommended level of exposure is 25 parts per million per procedure over an eight-hour period [109]. Sufficient fresh air flow in the procedural area is required, along with a secure fitting of the delivery mask. Nitrous is highly diffusible and will enter into closed spaces very easily.

For a short period, prehospital paramedics were using 50% nitrous oxide as an analgesic during stabilization and transport of patients to the hospital; however, this use did not gain traction, and nitrous oxide is not a universal requirement for emergency medical vehicles [110].

As with other analgesics, nitrous oxide tanks should be secured, as there is a potential for abuse and diversion, particularly in locations in which small tanks are used and can easily be removed and transported. Nitrous oxide also enhances combustion, so care should be taken when using it around lasers and electric cautery. This agent is associated with increased rates of postoperative nausea and vomiting, but the risk decreases with the duration of administration.

ANTIDEPRESSANTS

Antidepressants, including tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors (MAOIs), are now a mainstay of pain management. Each of these agents increases the circulating level of neurotransmitters (e.g., norepinephrine, serotonin, dopamine, acetylcholine) in the brain [111]. Note that while these agents have been used for pain management in some cases for decades, this use is often still considered to be off label [111].

Antidepressants act in the brain at the periaqueductal grey, the amygdala, the prefrontal cortex, the thalamus, and the somatosensory cortex, among other places [112]. However, they also work in the periphery, primarily by blocking voltage-gated Ca2+ channels, especially in the dorsal horn of the spinal cord. As discussed, when Ca2+ cannot enter a neuron, then exocytosis of neurotransmitters onto the receptors of the next order neuron cannot take place. This, in turn, blocks the transmission of the action potential and thus the painful stimulus [112]. Antidepressants also increase the effectiveness of endogenous GABA, an inhibitory neurotransmitter. The various antidepressant classes have different effects on pain pathways.

Tricyclic Antidepressants

TCAs are widely used in neuropathic pain. A TCA's mechanism involves blocking pre-synaptic reuptake of norepinephrine and serotonin; inhibition of neuronal membrane ion channels by reducing neuronal influx of calcium or sodium ions; and activity with adenosine and NMDA receptors [79]. A primary site of analgesic action is the descending modulatory pathway, where monoamine reuptake inhibition elevates norepinephrine and serotonin levels to enhance endogenous nociceptive inhibition. The secondary amines nortriptyline and desipramine are favored over the tertiary amines amitriptyline and imipramine due to more benign side effect profiles [113; 114]. Amitriptyline is often the treatment of choice for neuropathic pain [79]. Unfortunately, TCAs have numerous side effects, including xerostomia (dry mouth), tachycardia, urinary retention, and drowsiness [111].

Selective Serotonin Reuptake Inhibitors (SSRIs)

SSRIs were designed to treat depression by increasing the amount of circulating serotonin in the brain. This increased amount of serotonin results in down-regulation (decreased number and density) of the 5-HT receptors, which allows for an increased firing of serotonergic neurons in the brain [111]. Compared with the other antidepressants, SSRIs have limited utility in treating pain and are seldom prescribed for this purpose.

Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)

The dual serotonergic and noradrenergic re-uptake inhibitors (SNRIs) duloxetine, venlafaxine, and milnacipran are widely used in the treatment of neuropathic pain conditions. Duloxetine is used in painful diabetic neuropathy, with demonstrated efficacy at 60–120 mg/day. Venlafaxine behaves like a SSRI at doses of ≤150 mg/day and like an SNRI at doses >150 mg/day; a dose ≥150 mg/day is often necessary to achieve pain control [76]. Of the three available SNRIs, milnacipran has the greatest affinity for norepinephrine, duloxetine has the greatest potency in blocking serotonin, and venlafaxine selectively binds to the serotonin but not the norepinephrine transporter [115].

SNRIs are better tolerated than TCAs because they lack affinity for cholinergic, histaminic, and adrenergic receptors [89]. The anti-nociceptive effect of the SNRIs duloxetine and milnacipran primarily involves increasing serotonin and norepinephrine concentrations in descending inhibitory pain pathways, which enhances the suppression of afferent spinal inputs and reduce pain [113].

Monoamine Oxidase Inhibitors (MAOIs)

MAOIs work by irreversibly degrading the monoamine oxidase enzymes responsible for degrading norepinephrine. These agents, however, have numerous side effects, including hypotension, dizziness, headache, xerostomia, palpitations, and weight gain [116]. One potential issue is the interaction of MAOIs with tyramine and tryptophan. With oral ingestion, MAOIs inhibit the catabolism of dietary amines. When foods containing tyramine (e.g., red wine, aged cheeses and meats, soy sauce, tap beer, smoked or pickled fish, sauerkraut) are consumed, the individual may suffer from hypertensive crisis. If foods containing tryptophan (e.g., milk, poultry, tofu, nuts, seeds) are consumed, hyperserotonemia may result. The amount required to cause a reaction varies greatly from individual to individual and depends on the degree of inhibition, which in turn depends on dosage and selectivity. These side effects limit the utility of MAOIs in pain management [116; 117].

USING MULTIMODAL PAIN THERAPY: EXAMPLES FROM THE PROFESSIONAL LITERATURE

Which agents are appropriate for mild pain according to the WHO analgesic ladder?

With a clear understanding of the pharmacologic tools available to help manage pain, clinicians can begin the process of creating and supporting a pain management plan for each patient's unique needs. The World Health Organization (WHO) analgesic ladder, introduced in 1986 and disseminated worldwide, remains recognized as a useful educational tool but not as a strict protocol for the treatment of pain. It is intended to be used only as a general guide to pain management [118]. The three-step analgesic ladder originally intended for management of cancer-related pain designates the type of analgesic agent based on the severity of pain (***Figure 7***) [118]. Step 1 of the WHO ladder involves the use of nonopioid analgesics, with or without an adjuvant (co-analgesic) agent, for mild pain (pain that is rated 1 to 3 on a 10-point scale). Step 2 treatment, recommended for moderate pain (score of 4 to 6), calls for a weak opioid, which may be used in combination with a step 1 nonopioid analgesic for unrelieved pain. Step 3 treatment is reserved for severe pain (score of 7 to 10) or pain that persists after Step 2 treatment. Strong opioids are the optimum choice of drug at Step 3. At any step, nonopioids and/or adjuvant drugs may be helpful.

EVIDENCE-BASED PRACTICE RECOMMENDATION

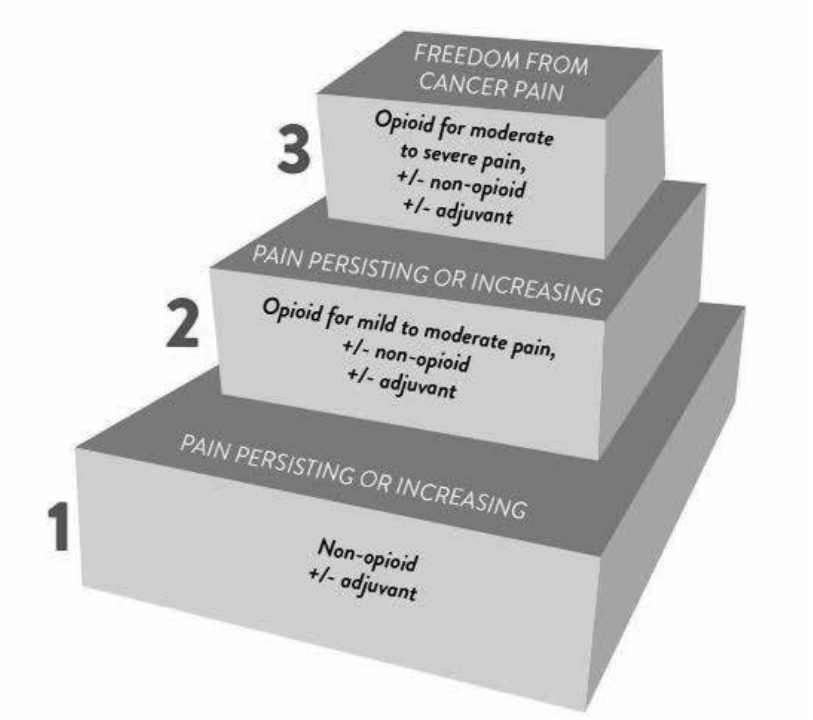
The Orthopaedic Trauma Association Musculoskeletal Pain Task Force recommends the use of multimodal analgesia (MMA) as opposed to opioid monotherapy for pain control. MMA may include NSAIDs, acetaminophen, gabapentinoids, and immediate-release opioids.

(https://journals.lww.com/jorthotrauma/fulltext/2019/ 05000/clinical_practice_guidelines_for_pain_management.11.aspx. Last accessed October 20, 2022.)

Strength of Recommendation/Level of Evidence: Strong recommendation, moderate-quality evidence

The pharmacologic treatment of pain involves selecting the right drug(s) at the right dose, frequency, and route, and managing side effects As with any healthcare action, it is vital to assess patients and to attempt to identify underlying cause(s) prior to the initiation of treatment. Specific evaluative steps should be taken to determine the nature of a patient's pain and to assess the possibility and impact of adverse effects. The WHO ladder is also accompanied by guiding principles [118; 119]:

THE WORLD HEALTH ORGANIZATION'S THREE-STEP LADDER OF ANALGESIA



Source: [118] *Figure 7*

- Believe the patient's report of pain. This sounds simple, but it can be difficult for clinicians to avoid becoming jaded over time, especially if they care for patients in drug-seeking environments.
- Initiate discussions of pain by asking specific questions and observing behaviors, such as groaning, a furrowed brow, and elevations in pulse or blood pressure.
- Get the facts about the pain. A helpful mnemonic taught to prehospital providers is OPQRST:
  - **O**nset
  - **P**rovocation or palliation
  - **Q**uality
  - **R**egion (of the body) and radiation
  - **S**everity
  - **T**iming
- Evaluate the patient's psychological state.
- Perform a detailed physical assessment.
- Obtain further testing if one is not sure, including radiologic and laboratory tests.

With these data, the provider is now ready to plan and carry out multimodal analgesia. The following examples are presented as examples of the applicability and efficacy of multimodal approaches in research studies.

EXAMPLE 1

In one study, 150 patients were assessed for breakthrough pain following shoulder surgery [120]. The first group (75 patients) was given a standard course of opioid and acetaminophen combination (hydrocodone 10 mg/acetaminophen 325 mg) or 5–10 mg of oxycodone every 4 hours [120]. They also received a single-shot interscalene regional nerve block with 0.5% ropivacaine (local anesthetic). Finally, intravenous hydromorphone was also available as a rescue intervention. In the second multimodal group (75 patients), patients received preoperative 300 mg celecoxib, 600 mg gabapentin, and 1,000 mg acetaminophen. They also received the same regional nerve block. For postoperative pain, group 2 received naproxen 500 mg every 12 hours with food, gabapentin 300 mg every 8 hours, acetaminophen 1,000 mg orally or IV, followed by 500 mg orally every 6 hours. For breakthrough pain, this group could receive 5–10 mg of hydrocodone, as needed [120]. There were no differences in the demographic makeup of the two groups.

On postoperative day zero (the day of surgery), pain scores were significantly lower in group 2 when compared with the standard group [120]. On postoperative days 1 and 2, the multimodal group continued to have lower scores, but the differences were not statistically significant. Opioid consumption, measured in mg of morphine equivalent, were significantly decreased in the multimodal group on all three measurement days. The length of in-patient stay for the multimodal group was significantly lower (1.4 days +/- 0.7) compared with the opioid group (1.9 days +/- 1.1 days), resulting in an average cost savings of $1,000 for the multimodal group [120].

EXAMPLE 2

In this study, patients with unresectable hepatocellular carcinoma received transarterial chemoembolization, a primary palliative treatment [121]. This group of patients have chronic pain, and transarterial puncture is associated with a lower degree of surgical pain. In this example, patients are provided with a therapeutic procedure that can partially mitigate the pain and then supported with other analgesic agents. The study involved a total of 84 patients, with half assigned to the multimodal group and the other half assigned as a control group [121].

The multimodal group received 40 mg intravenous parecoxib sodium 30 minutes before the beginning of the procedure. In the control group, patients received 5 mg dezocine (an opioid) preintervention. All patients underwent a percutaneous puncture of the femoral artery after having the site numbed with 10 mL 2% lidocaine (total dose: 200 mg lidocaine). After the procedure, the multimodal group was provided with a patient-controlled analgesia pump; the intravenous pain solution was a combination of sufentanil 100 mcg and dexmedetomidine 200 mcg diluted in 100 mL normal saline. The pump was programmed to provide 2 mL of the solution (2 mcg of sufentanil and 4 mcg of dexmedetomidine) as a first dose, a background infusion rate of 2 mL/hour, and 2 mL bolus doses on demand with a lockout period of 5 minutes (maximum: about 12 doses per hour) [121]. This sufentanil dose is below the usual administered for general anesthesia. The dose of dexmedetomidine tracks closely to that needed for intensive care unit (ICU) sedation [122]. Using the two agents together provides central sedation via two routes (one from the opioid, the other from the alpha-2 agonist) while simultaneous providing pain relief throughout the spinal cord.

The control group received 100 mg flurbiprofen (an NSAID) every 12 hours for the first 48 hours postprocedure and 100 mg tramadol (a combination opioid agonist and SSRI) for breakthrough pain [121]. Mean visual analog scale (VAS) pain scores were measured at 0, 2, 4, 6, 12, 24, and 48 hours after the procedure. Patients in the multimodal group had statistically lower VAS pain scores at 0, 2, 4, 6, and 12 hours after the procedure. From a qualitative viewpoint, more than 95% of the multimodal patients reported good satisfaction with their pain control. In the control group, 69% reported good satisfaction, and 11.9% reported a "fairly bad experience" of pain control [121].

CASE STUDIES

The following case examples detail how specific patients were cared for and the logic behind analgesic decision-making. This should serve as a starting point that will result in further self-exploration.

CASE STUDY 1

Note that this first example is directed toward the management of acute pain, and the interventions take place in the hospital or surgical facility. Many people, however, suffer chronic pain and self-medicate to treat it. In either case, multimodal analgesic techniques may still be used.

Patient A is scheduled to receive a total knee replacement arthroplasty [123]. Preoperatively, the patient is counseled regarding what pain might be expected with this surgery and how it might be treated. After the patient has been worked up, she receives acetaminophen 1,000 mg and celecoxib 400 mg by mouth [123]. This is referred to as pre-emptive analgesia and is done to ensure that the processes needed to, in this case, block the inflammatory effects of prostaglandins released by surgery are beginning to function prior to initiation of surgery [124].

The patient is next taken to a block room and receives local anesthesia in the knee area. In other cases, surgeons may inject local anesthesia at the end of the case.

During surgery, the patient receives a spinal anesthetic with local anesthesia. The anesthetic is placed in the subarachnoid space with local anesthesia. Because the local anesthetic is deposited so close to the nerves, a very small dose can provide several hours of anesthesia.

After surgery, the patient begins to receive several pain management interventions almost immediately, the first of which is cryotherapy. Next, as the body is responding with an inflammatory process releasing prostaglandins and other neurotransmitters in response to an injury (albeit a therapeutic one), the patient receives 1,000 mg of acetaminophen every six hours around the clock [123]. This patient tolerated oral analgesics, but acetaminophen can be administered intravenously for those experiencing problems with postoperative nausea and vomiting. The patient is also started on celecoxib 200 mg twice per day for up to five days. At this point, Patient A begins to question the need for NSAIDs when she is "having no pain." The nurse describes the importance of reducing inflammation in simple terms. He also explains that the long-acting local anesthetics will wear off over time, and it is important to pre-emptively control pain. Despite these interventions, some patients will experience postoperative pain exceeding the ability of NSAIDs to mitigate. For these individuals, an opioid rescue (oxycodone tablet 5 mg and intravenous hydromorphone 0.2 mg) every four hours as needed will help bring most pain under control [123].

CASE STUDY 2

Patient B is an elderly man (85 years of age) with chronic and unremitting pain. Initial assessment of the patient's pain remains important. While Patient B is experiencing chronic pain, he may also have an unresolved injury or illness causing the pain. In such a case, treatment of the underlying pathology could result in mitigation of pain [125].

Therapeutic intervention for Patient B begins with the use of NSAIDs and COX-2 inhibitors, especially for a pathology such as osteoarthritis, which is quite common among the elderly. As part of the assessment in this example, remember that elderly patients tend to have less total body water, decreased muscle tone, increased fat stores, and normal age-related degeneration of the liver and kidneys [125]. Unless there are other factors (e.g., current opioid use disorder), the best approach is to start low and titrate slow—use the smallest dose possible and increase it incrementally in small doses. The elderly often experience depression as part of their chronic pain; this should not be surprising, as living with unresolved pain each day can be psychologically taxing. Antidepressant agents, such as an SNRI, may be added to the care plan, with the caveat that there is an increased risk of falling [126]. Gabapentinoids may replace the antidepressant if the pain is neuropathic in nature, and opioids can be added on an as needed basis, though it is crucial to start at the low end of the dosing scale [126]. This follows the WHO guidance of NSAIDs first and opioids last.

While it is fine to conduct mental exercises with imaginary patients, the guiding standard for the clinician is whether the analgesia works. This is an important question, so at this point a small number of studies will be presented for your review.

CASE STUDY 3

In this example, Patient C, a man 71 years of age, presents with a severe case of recurring right sciatic pain [127]. On history and examination, the patient describes persistent pain at a scale of 8 out of 10, starting in the lumbar area of his back and running down his right thigh. Further comorbidities include chronic obstructive pulmonary disease (COPD) and previous right-side neck surgery to remove a buccal tumor. An MRI is ordered, revealing spondylolisthesis, which causes pain in lower back or legs at L5–S1, and the patient was also identified as having degenerative disk disease at L5–S1, and disk herniations at L3–L4, L4–L5, and L5–S1 [127]. This patient is taking 20 mg oxycodone daily in an effort to mitigate his pain.

The pain control team begins to titrate back the patient's oxycodone with tramadol and offers surgical decompression. After the patient refuses surgical intervention, the team decides to administer an ultrasound-guided caudal epidural steroid injection of triamcinolone 40 mg and 2% lidocaine 20 mg (local anesthetic) mixed in 12 mL of normal saline [127]. The mixture of normal saline is necessary because epidural injections require a greater volume to ensure the nerve roots are all bathed in the solution.

After the injection, Patient C's walking distance increases from 20 meters to 200 meters, and his pain score reduces from 10 to 7. One month later, the patient remains improved, but the team decides to add 5 mg oxycodone (25% of the original dose) as needed back to the patient's regimen. By his third month post procedure, the patient's pain score has dropped to 2. The multimodal plan, when compared with the singular large dose opioid plan, proved to be life-changing for this patient [127].

CONCLUSION

It is important to remember that pain is an adaptive mechanism to protect the body from comprise and prevent future involvement with the pain-generating stimulus. Modern medicine has many options to identify causes of pain and to treat the underlying problem while providing relief from pain [27]. However, pain management is an elusive goal for many patients. In the 1990s and 2000s, in an effort to address this problem, opioids were prescribed more freely. Unfortunately, this corresponded with an increase in opioid misuse and use disorder. In order to both assure that patient pain is managed and reduce the risks associated with opioids, numerous types of analgesics and techniques can be carefully mixed to decrease side effects while optimizing pain control.

It is crucial for all practitioners to carefully evaluate patients who are in pain to determine the extent to which the pain can be repaired or relieved. All available tools should be explored to treat the causes of pain at the local peripheral levels, the spinal cord levels, and the brain processing level. Familiarity with the pathophysiology of pain can guide good pharmacologic decisions and restore the patient's quality of life.

Customer Information/Evaluation insert located between pages 32–33.

Pancreatic Cancer

Includes 9 Pharmacotherapeutic/Pharmacology Hours

Audience

This course is designed for nurses, physicians, and other members of the interprofessional healthcare team involved in the care of patients with pancreatic cancer.

Course Objective

The purpose of this course is to provide healthcare professionals with the knowledge and skills necessary to recognize and appropriately manage pancreatic cancer in their patients.

Learning Objectives

Upon completion of this course, you should be able to:

1. Outline the epidemiology of and risk factors for pancreatic cancer.
2. Describe the pathophysiology of pancreatic cancers.
3. Discuss recommendations for screening for pancreatic cancer in various patient populations.
4. Describe key aspects of the clinical evaluation of patients with suspected pancreatic cancer.
5. Select the appropriate tools for diagnosis and staging of pancreatic cancer.
6. Apply models of assessing the functional performance status of patients with diagnosed pancreatic cancer.
7. Discuss the role of resection in pancreatic cancer treatment, including most appropriate approaches.
8. Compare and contrast chemotherapy regimens used in the treatment of pancreatic cancer.
9. Describe the use of radiation therapy as a component of pancreatic cancer treatment according to evidence-based guidelines.
10. Evaluate available interventions to manage symptoms and provide palliative care to patients with pancreatic cancer.

Faculty

Mark Rose, BS, MA, LP, is a licensed psychologist in the State of Minnesota with a private consulting practice and a medical research analyst with a biomedical communications firm. Earlier healthcare technology assessment work led to medical device and pharmaceutical sector experience in new product development involving cancer ablative devices and pain therapeutics. Along with substantial experience in addiction research, Mr. Rose has contributed to the authorship of numerous papers on CNS, oncology, and other medical disorders. He is the lead author of papers published in peer-reviewed addiction, psychiatry, and pain medicine journals and has written books on prescription opioids and alcoholism published by the Hazelden Foundation. He also serves as an Expert Advisor and Expert Witness to law firms that represent disability claimants or criminal defendants on cases related to chronic pain, psychiatric/substance use disorders, and acute pharmacologic/toxicologic effects. Mr. Rose is on the Board of Directors of the Minneapolis-based International Institute of Anti-Aging Medicine and is a member of several professional organizations.

Faculty Disclosure

Contributing faculty, Mark Rose, BS, MA, LP, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Division Planner/Director Disclosure

The division planner and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the study questions and course material for better application to your daily practice.

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) has the worst prognosis of any common cancer. The five-year overall survival rate is approximately 10% and has improved only marginally in five decades [1]. There are four fundamental challenges that underlie the high mortality of PDAC: pancreatic anatomy, aggressive biology, systemic effects, and treatment resistance.

The retroperitoneal position of the pancreas is situated deep within the upper abdomen, behind the stomach, and between the aorta and its major upper abdominal branches. Shielded from detection, the tumors often grow around and encase these vessels, making the cancer inoperable in nearly 85% of patients [2]. With this aggressive cancer, more than 50% of patients have distant metastases at diagnosis, and micrometastases are already present in most patients undergoing resection for apparently localized tumors [2; 3; 4].

At diagnosis, up to 80% of patients with PDAC present with cachexia, a wasting syndrome and physiologic effect of PDAC. Cachexia dramatically weakens patients, limiting their ability to withstand aggressive treatment. The poor treatment tolerance of patients with cachexia is evidenced by decreased survival after resection or chemotherapy [2].

The complex tumor microenvironment and heterogeneity of gene mutations make PDAC one of the most drug-resistant cancers. Most treatment options are ineffective, with rapid progression and low complete responses to the most effective chemotherapy and radiotherapy [1; 4].

Surgical resection of the pancreas with microscopically free margins (R0 resection) followed by chemotherapy remains the only realistic option for remission, but this is potentially achievable in only a fraction of patients [4; 5]. Nonetheless, incremental gains have been increasingly frequent over the past decade, and more substantive gains are anticipated, pending clinical trial results. This course will describe the current standard of care for patients with pancreatic cancer and present information that may help increase earlier detection of this malignancy and improve the symptom burden and quality of life in these patients, regardless of disease stage.

Clinical practice guidelines for patients with pancreatic cancer have been published by the American Society of Clinical Oncology (ASCO), the NCCN (National Comprehensive Cancer Network), the American Society for Radiation Oncology (ASTRO), the European Society for Medical Oncology (ESMO), the National Institute for Health and Care Excellence (NICE), and others [6; 7; 8; 9; 10; 11; 12; 13; 14; 15]. The recommendations are largely concordant on what constitutes multidisciplinary standards of care in the management of pancreatic cancer [2; 16].

PANCREATIC CANCER STAGE AT DIAGNOSIS AND ASSOCIATED SURVIVAL		
Stage	**Progression at Diagnosis**	**Five-Year Survival**
Localized	11%	41.6%
Regional	30%	14.4%
Distant	52%	3.0%
Unknown	7%	6.5%

Source: [19] *Table 1*

Most pancreatic cancers arise in the exocrine pancreas (95%). Tumors of the endocrine pancreas (<5%) are distinct from exocrine pancreas cancers and will not be discussed in this course [4].

PDACs account for more than 95% of exocrine pancreatic cancers. PDAC and pancreatic cancer are commonly used as interchangeable terms in the literature and will be in this course [17].

EPIDEMIOLOGY

What is the median age at diagnosis of pancreatic cancer?

During 2021 in the United States, an estimated 60,430 people will be diagnosed with pancreatic cancer, which represents 3.2% of all new cancer cases and the 11th most common new cancer diagnosis. The median age at diagnosis is 70 years [18].

Approximately 1.7% of men and women will be diagnosed with pancreatic cancer at some point during their lifetime, based on 2016–2018 data. In 2018, an estimated 83,777 people were living with PDAC in the United States [19].

With an estimated 48,220 deaths in 2021, pancreatic cancer is the third leading cause of cancer death (after lung and colorectal cancer) in both men and women; it is expected to become the second leading cause of cancer death by 2030 [2; 19; 20]. The median age at death is 72 years [18].

Pancreatic cancer stage at diagnosis strongly influences the length of survival, as shown by data from 2011 to 2017 (***Table 1***) [19]. The five-year survival of PDAC, 10.8%, remains the lowest of all common cancers [19; 21].

During 2013–2017, annual pancreatic cancer incidence and mortality rates (per 100,000 persons) were higher among men (14.9 and 12.7) than women (11.6 and 9.6). These rates were highest for Blacks (15.3 and 13.3), followed by non-Hispanic Whites (13.1 and 10.9) and Hispanics. The rates were lowest for Asian/Pacific Islanders and American Indian/Alaska Natives [2].

Since 2010, both incidence and mortality rates increased by an average of 0.3% per year. Underlying these trends is a combination of an aging population, a longer lifespan, and the high prevalence of obesity and diabetes [11; 18]. In 2015, lost earnings from person-years of life lost from pancreatic cancer were estimated at more than $6 billion [2].

RACIAL SURVIVAL DISPARITIES

In examining PDAC survival disparities over 2004–2015, the unadjusted median overall survival was slightly longer for White patients than Black patients (6.6 months vs. 6.0 months). Decreased survival for Black patients persisted after controlling for sociodemographic parameters. Conversely, controlling specifically for clinical parameters (e.g., disease stage, treatment) found a modest survival advantage for Black patients [22].

Black patients with PDAC present at younger ages with more advanced disease than White patients, possibly suggesting differences in tumor biology. Black patients receive less treatment stage-for-stage and fewer surgeries for resectable PDAC than White patients; these findings may be only partly associated with socioeconomic differences. In one study, when disease stage and treatment were controlled for, Black patients had no decrease in survival compared to other races [22].

Role of Implicit Bias

Health professionals' implicit biases shape behaviors, communications, and interactions, which then produce differences in diagnoses and ultimately treatments and interventions. Implicit biases are subtle and unconscious and may unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider.

Racial and socioeconomic differences in surgical intervention rates, treatment at high-volume hospitals/centers, and morbidity and mortality rates have been noted, with the largest disparities between Black (and to a slightly lesser extent Hispanic) and White Americans [23]. Several factors are implicated, but implicit biases and insurance status are identified as potentially modifiable contributors.

COMMON RISK FACTORS FOR THE DEVELOPMENT OF PANCREATIC CANCER	
Factor	**Relative Risk**
Cigarette smoking	1.7-fold to 2.6-fold
Obesity	1.1-fold to 1.5-fold
Diabetes	1.5-fold to 2-fold
Family history	1.7-fold to 2.3-fold
Chronic pancreatitis	13.3-fold
Source: [2]	*Table 2*

NON-GENETIC RISK FACTORS

The most common recognized risk factor for pancreatic cancer is cigarette smoking followed by obesity. Others include pancreatitis, diabetes, and family history of pancreatic cancer (***Table 2***) [13; 24]. Periodontal disease is increasingly linked to pancreatic and other gastric cancers. Chronic pancreatitis substantially elevates the risk of developing pancreatic cancer and represents an opportunity for surveillance and monitoring. Most importantly, new-onset hyperglycemia or diabetes is now recognized as an early symptom of PDAC in an otherwise asymptomatic patient. Many recognized risk factors are modifiable for prevention of pancreatic cancer.

Smoking

Cigarette smokers have at least a two-fold greater risk for pancreatic cancer than nonsmokers. The risk increases with the amount of cigarettes consumed and duration of smoking. In heavy smokers with polymorphism in the carcinogen-metabolizing enzyme gene glutathione S-transferase theta 1 (*GSTT1*), the risk is up to five-fold greater [25; 26].

Excess risk decreases with smoking cessation. The risk of pancreatic cancer among current smokers (relative risk: 2.5) decreased 48% two years after smoking cessation, and within 10 to 15 years after cessation, it approximated that of nonsmokers [26].

In the United States, estimates indicate that 11% to 32% of deaths from PDAC are attributable to tobacco smoking. It is estimated that cessation of smoking could eliminate up to 25% of pancreatic cancer deaths [24; 26].

Alcohol Consumption

Limited evidence suggests alcohol consumption may be associated with risk of developing PDAC, but findings of population-based studies are inconsistent. In pooled cohort data of 1.5 million light, heavy, or never-drinkers, heavy drinkers had a greater relative risk of developing PDAC than never-drinkers (relative risk: 1.29) or light drinkers (relative risk: 1.36). Light drinkers had no difference compared to never-drinkers (relative risk: 0.96) [27].

Smoking and Drinking

Most studies have assumed additivity between average effects of smoking and alcohol and oversimplified their impact on burden of pancreatic cancer. However, the combined effect of smoking and total alcohol intake on risk of PDAC is likely non-additive. It appears that only heavy consumption of liquor (but not wine or beer) increases the risk of PDAC in ever-smokers [27].

Obesity

A number of studies have associated obesity with a higher incidence of pancreatic cancer. Obesity (defined as a body mass index [BMI] >30) during early adulthood was associated with a greater risk of PDAC and younger age of disease onset. Tumorigenesis is enhanced by excess adipose tissue. Obesity is associated with a 20% to 40% higher mortality rate from PDAC, and obesity at an older age is associated with lower overall survival [13; 28].

Although BMI is widely used as a marker for general adiposity, visceral obesity has a stronger correlation to metabolic syndrome, insulin resistance, and certain gastrointestinal (GI) malignancies. The close proximity to visceral organs and drainage via the portal system may explain the strong correlation of inflamed visceral adipose tissue (VAT) in obese subjects with metabolic dysfunction and pancreatic cancer [29].

Diet

There is some evidence that higher consumption of red/processed meat is associated with elevation in pancreatic cancer risk, but other studies have failed to identify dietary risk factors for PDAC [11]. Pancreatic cancer incidence may be lower in persons with higher intake of fresh fruits and vegetables rich in folate and lycopenes (e.g., tomatoes) [30].

A link between vitamin D and risk for pancreatic cancer is inconsistent, but some data suggest low plasma 25-hydroxyvitamin D levels may increase the risk for pancreatic cancer, especially in those with low retinol/vitamin A intake [31]. Coffee and tea consumption are not associated with pancreatic cancer risk, despite early reports to the contrary [24].

Systemic/Nonmodifiable Risks

Numerous studies and meta-analyses have found systemic/nonmodifiable factors that increased the relative risk, hazard ratio, or odds ratio of developing pancreatic cancer. These include individuals with greater height (relative risk: 1.81); individuals with blood groups A, AB, and B (hazard ratio: 1.32, 1.51, and 1.72, respectively); and patients with hepatitis B infection (odds ratio: 1.50) or systemic lupus erythematosus (hazard ratio: 1.43). Biologic explanations for some of these associations are not yet understood, and some data may have potential confounders. Infectious etiologies warrant more investigation [11; 32].

Periodontal Disease

Periodontitis describes a chronic inflammatory response to a disease-associated, multispecies bacterial community in the subgingival region. Periodontal disease is associated with pancreatic cancer, even when controlling for gender, smoking, BMI, diabetes, and alcohol consumption [33]. The inflammatory processes of periodontitis occur locally, but systemic dissemination of inflammatory mediators, subgingival species, and bacterial components contribute to digestive cancers (including PDAC) by activating proinflammatory pathways, inducing gene expression related to cell proliferation, apoptosis, and immune responses linked to carcinogenesis, cell migration, invasion, and metastasis [34].

Chronic Pancreatitis

A high-risk subgroup for PDAC are patients with chronic pancreatitis, often secondary to chronic alcohol use disorder, smoking, hypertriglyceridemia, diabetes, or renal failure [2]. Patients with chronic pancreatitis show a 26-fold increase in risk of developing PDAC. This risk increases with duration. Among patients with chronic pancreatitis of 20 years' duration, approximately 5% will progress to PDAC.

Concomitant smoking enhances the risk of neoplastic progression [2; 35]. Hereditary pancreatitis further increases the risk of pancreatic cancer by more than 50-fold. In these individuals, the cumulative risk of pancreatic cancer by age 70 years is 40% [24].

Long-Standing Diabetes

Pancreatic cancer has complex relationships with diabetes and obesity that are only recently becoming understood. A population cohort study underscored the complex relationship between metabolic abnormalities and PDAC. Glycemic status, insulin resistance, and hyperinsulinemia were independently associated with an increased risk of pancreatic cancer mortality, even in individuals without diabetes [36].

The association between pancreatic cancer and diabetes was noted as early as 1833, clearly documented by the 1930s, and characterized in a large cohort of patients with pancreatic cancer from Mayo Clinic in 1958 [37]. Several meta-analyses have greatly refined the risk-factor status of diabetes.

Long-standing (i.e., more than five years) diabetes (both type 1 and type 2) is associated with increased risk of developing PDAC [13]. The overall risk for PDAC increases 4- to 7-fold in those with diabetes of a duration less than three years [38]. The relative risk associated with diabetes levels off after five years, with a 1.5-fold greater risk [39]. Increased baseline hemoglobin A1C (HbA1C) levels correlate with subsequent development of PDAC [40].

Long-standing diabetes modestly increases the risk of PDAC, which decreases with diabetes duration [11; 37]. The initial three-year period after diabetes diagnosis is high risk for PDAC, as confirmed by prospective pancreatographic screening [41].

With diabetes medications, insulin use has been associated with increased risk of PDAC, but this finding is attributed to reverse causality [11; 42]. Metformin use in patients with diabetes and PDAC was associated with improved two-year survival (30.1% vs. 15.4%) and median overall survival (15.2 months vs. 11.1 months) in patients without metastases [43]. One metformin study reported negative findings [44].

Long-standing diabetes in patients who develop PDAC is associated with significantly lower overall survival (14.4 months vs. 21.7 months) and significantly higher mortality (harm ratio: 1.52) compared with patients without diabetes who develop PDAC [11; 45].

Postpancreatitis Diabetes Mellitus

Diabetes of the exocrine pancreas (formerly type 3c diabetes) is the second most common type of new-onset diabetes in adults (behind type 2 diabetes) [42]. Acute or chronic pancreatitis is one of the most prevalent risk factors for PDAC and the most frequent cause of diabetes of the exocrine pancreas. Pancreatitis leads to postpancreatitis diabetes mellitus in up to 83% of patients [42]. In a registry study involving 139,843 individuals, the proportion of pancreatic cancer was 3.1% among those with postpancreatitis diabetes mellitus, compared with 2.3% in those with type 2 diabetes followed by pancreatitis, 2.0% in those with pancreatitis alone, and 0.6% in individuals with type 2 diabetes alone [42].

Prediagnostic Metabolic and Soft Tissue Changes

Numerous studies have identified new-onset diabetes, weight loss, and soft tissue changes in patients with PDAC at diagnosis, but their inter-relationship and connection to PDAC remained unaddressed. From 2000 through 2015, temporal changes in the five years preceding PDAC diagnosis of 219 patients diagnosed with PDAC were compared to 657 controls [46]. From 60 to 30 months before PDAC diagnosis, patients did not significantly differ from controls. However, starting at 30 months prediagnosis, PDAC showed three distinct metabolic phases, each marked by onset and significant progressive worsening of one or more metabolic abnormalities [46]:

- Phase 1, hyperglycemia (30 to 18 months before PDAC diagnosis): A significant proportion of patients develop hyperglycemia, without soft tissue changes.

- Phase 2, pre-cachexia (18 to 6 months before PDAC diagnosis): Decreases in serum lipids, weight loss, and the first soft tissue change (subcutaneous abdominal tissue loss) are seen. A profile appears of advanced prediabetes (i.e., fasting blood glucose 120–126 mg/dL or A1c of 6% to 6.5%). In type 2 diabetes, this is associated with weight gain and hyperlipidemia due to insulin resistance. In PDAC, decreases in weight and serum lipids despite rising glucose levels are paradoxical.
- Phase 3, cachexia (less than 6 months before PDAC diagnosis): Onset of muscle loss, visceral adipose tissue loss, and decreasing high-density lipoprotein. Continued decreases in all other serum lipids, subcutaneous abdominal tissue, and weight. Fasting blood glucose continues rising.

Based on evidence of increases in body temperature before PDAC diagnosis, browning and loss of subcutaneous abdominal tissue is estimated to begin 18 months before PDAC. Browning of white abdominal tissue is a mechanism of subcutaneous abdominal tissue loss in cancer; its purpose is to generate heat [46].

Symptoms of cachexia and muscle loss (e.g., anorexia, fatigue, reduced exercise tolerance) appear shortly (less than six months) before PDAC diagnosis. The onset of objective weight loss precedes PDAC diagnosis by one year or more. New-onset diabetes appears a median of six to nine months before PDAC diagnosis [46].

Pancreatic Cancer Cachexia and Diabetes

Cancer cachexia is a paraneoplastic syndrome characterized by pronounced weight loss and muscle wasting triggered by cancer-induced systemic inflammation [47]. Cachexia develops in about 80% of patients with PDAC during the disease course, often before the tumor is clinically apparent. Cachexia negatively impacts treatment response and survival, and one-third of patients with PDAC die from cachexia-associated complications, including impaired immunity and cardiopulmonary dysfunction. No curative treatments exist [47].

Pancreatic cancer-associated diabetes mellitus might be a major contributor to PDAC-induced cachexia. The co-occurrence is frequent, and the relationship between pancreatic cancer-associated diabetes and PDAC-induced cachexia was clarified in a 2020 study [47]. Compared with patients without pancreatic cancer-associated diabetes, those with pancreatic cancer-associated diabetes did not have a higher risk of cachexia, a greater degree of weight loss, or lower skeletal muscle mass. Among patients with cachexia, weight loss and skeletal muscle mass were comparable between patients with and without pancreatic cancer-associated diabetes. Fasting blood glucose levels and PDAC-derived diabetogenic factors did not correlate with weight loss or muscle mass or predict cachexia in patients with pancreatic cancer-associated diabetes. A notable finding was the consistently high prevalence of cachexia and muscle wasting regardless of tumor size and stage in PDAC [47]. These results argue against pancreatic cancer-associated diabetes and hyperglycemia in mediating PDAC-induced cachexia.

Cancer cachexia is characterized by systemic inflammation with resultant skeletal muscle breakdown and increased circulating amino acids to support tumor growth. Pancreatic cancer-associated diabetes is a metabolic strategy by PDAC to fuel tumor growth. PDAC cells have a high demand for glucose (termed "glucose addiction"); hyperglycemia promotes invasion and migration of PDAC cells. PDAC-induced cachexia and pancreatic cancer-associated diabetes are distinct metabolic reprogramming induced by PDAC cells to secure amino acids and glucose for tumor growth [47].

Unexplained weight loss/cachexia is a clue to occult PDAC, but a modality that can identify PDAC-induced cachexia is needed to take advantage of this screening opportunity [47]. Optimizing glycemic control may not alleviate weight loss or muscle wasting, and therapies targeting mediators of pancreatic cancer-associated diabetes may not protect against the development of cachexia [47]. Management of cachexia in patients with PDAC is discussed in detail later in this course.

PATHOPHYSIOLOGY

PDAC is caused by somatic (acquired) and germline (inherited) mutations in specific cancer-associated genes. In PDAC, the accumulation of multiple combinations of gene mutations significantly perturbs major signaling pathways, leading to a malignant phenotype [13; 48; 49; 50].

Like most solid tumors, PDACs are driven by mutations that disrupt intra- and extracellular networks that normally restrain abnormal growth, proliferation, survival, and invasion [51]. Four major genetic drivers are fundamental in nearly all PDACs. These involve mutational activation of the oncogene *KRAS*, and mutational inactivation of the tumor suppressor genes *CDKN2A*, *TP53*, and *SMAD4* [3; 50; 52; 53]. Inactivation of genome maintenance genes that repair DNA damage is a third broad type of mutation in PDAC.

PRIMARY MUTATIONAL DRIVERS IN PDAC

KRAS encodes a GTPase molecule that acts as a transducer for growth factor receptors on the cell surface. *KRAS* mutations dysregulate intrinsic GTPase activity, stimulating downstream pathways that drive uncontrolled cellular proliferation, angiogenesis, suppression of apoptosis, and evasion of immune response [54].

CDKN2A encodes the proteins p16 and p14ARF, which are both cell-cycle regulators. With loss of *CDKN2A* gene function, inactivation of p16 results in unchecked cell cycle progression and enhanced tumor cell proliferation [3; 49]. *TP53* encodes the protein p53, called the "guardian of the genome," which plays a central role in DNA repair, cell cycle arrest, and induction of apoptosis in response to DNA damage or cellular stress [55].

Inactivation of p53 (loss of function mutation) allows DNA damage to go unchecked with failed apoptosis and unregulated G1/S cell cycle transition. Mutant p53 can also gain pro-oncogenic activities (gain-of-function mutation), promoting cell proliferation, survival, angiogenesis, and metastases [54].

SMAD4 encodes the protein Smad4, a downstream effector of transforming growth factor-beta (TGF-b) signaling pathway. *SMAD4* inactivation and loss of Smad4 promotes cancer progression by removing the early growth inhibitory effect of the TGF-b pathway and is associated with higher rates of distant metastasis and poorer prognosis [54].

MUTATIONAL SEQUENCE OF PDAC DEVELOPMENT

What is the median age at diagnosis of pancreatic cancer?

Through pathways and somatic mutations that differ modestly in each lesion, PDAC develops from precancerous precursor lesions: pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasm (IPMN), and mucinous cystic neoplasms (MCNs). The most common are PanINs (approximately 90%), and the least common are MCNs. However, all precursor lesions have key similarities [4; 48; 50]:

- Early oncogene mutations initiate tumorigenesis.
- Later loss of tumor suppressor genes drive tumor progression, high-grade dysplasia, and invasive cancer.
- Increasing grades of dysplasia are associated with accumulation of somatic mutations in key driver genes.

Pancreatic Intraepithelial Neoplasia (PanIN)

PDAC develops in PanINs through a specific process [56]. First, mutational *KRAS* activation initiates pancreatic carcinogenesis. With tumor suppressor inactivation, cancer progresses. *CDKN2A* or *SMAD4* are implicated in locally destructive disease; *TP53* is involved in metastatic seeding; and concurrent *SMAD4* and *TP53* are often present in locally or metastatic dominant disease. IPMNs and MCNs often share the driver gene mutations and sequence of PanINs, but also show specific patterns.

Intraductal Papillary Mucinous Neoplasms (IPMN)

More than 90% of IPMNs are marked by activating mutations in the oncogene *GNAS* and/or inactivating mutations in the tumor suppressor gene *RNF43* [48; 53; 54]. *GNAS* mutation causes constitutive activation of adenylyl cyclase, with downstream effects driving proliferation. *RNF43* encodes E3 ubiquitin-protein ligase, which functions as a tumor suppressor in the Wnt-signaling pathway. After the initiating oncogene mutation, the progression of IPMN resembles PanIN.

Mucinous Cystic Neoplasms (MCN)

RNF43 mutation is also a prevalent event in MCNs (50%). As in PanINs, genetic changes accumulate with higher grade of dysplasia and invasiveness [48; 53; 54].

NATURAL HISTORY OF PDAC ONCOGENESIS

The PanIN Progression Model has been critical in shaping the perspective of how PDAC develops and progresses over the past two decades. PDAC arises through a specific sequence of genetic alterations over a gradual progression from early PanIN to late-stage metastatic disease [57; 58; 59].

The timeframe of PanIN progression has also been established. Based on computational modeling using autopsy cases, the estimated average time interval from initiation in normal cells to invasive ability (11.7 years), metastatic dissemination (6.8 years) and death (2.7 years) corresponds to an average of about 21 years from the initiating mutation until a patient's death [17].

Most cases with PDAC are diagnosed toward the end of this lifetime span, suggesting that poor prognosis is a result of late diagnosis in the natural history of PDAC, and that a golden opportunity of two or three years exists to diagnose "early" pancreatic cancer (i.e., Stage 0 or I) [60].

Chromothripsis, a recently identified phenomenon, is a catastrophic event causing tens to thousands of chromosomal rearrangements. Faced with hundreds of DNA breaks, the cell's DNA repair machinery attempts to rescue the genome, but the result bears little resemblance to its original structure [61; 62]. This genomic disruption can drive the development of cancer through DNA copy number changes, including deletion of tumor suppressor genes and increased copy number (amplification) of oncogenes [61].

A 2016 study of more than 100 whole genomes from pancreatic cancer tumors found evidence of at least one chromothripsis event in 65% of tumors, and most copy-number changes seemed to occur after such catastrophic genetic events. With evidence of chromothripsis in some PDACs and nongradual tumorigenesis that defies the established mutational sequence, a punctuated equilibrium model was proposed, dividing tumor development into two major events [63]:

- A cancer-initiating event: PDAC pre-neoplasms acquire extensive mutation burden but remain non-invasive over a prolonged preneoplastic phase.
- A cataclysmic cancer-transforming event: Chromothripsis induces DNA copy number changes, creating genomic instability and generating invasive clones with rapid dissemination and colonization of distant sites. Why chromothripsis occurs in PDAC is not yet understood.

Non-Genetic Mechanisms

Rather than being uniformly aggressive, PDAC demonstrates clinical (e.g., variable patient survival) and disease (e.g., variable chemotherapy sensitivity) heterogeneity [64; 65]. The first whole-genome description of PDAC in 2008 prompted great effort to advance a patient-tailored precision medicine approach that could better address this heterogeneity. Genetic alterations and molecular subtypes in PDAC were characterized and published. PDAC was shown mutationally dominated by the four driver genes and homogeneous. In general, the findings importantly informed the biology and familial predisposition of PDAC.

However, by 2019 it was apparent that PDAC disease heterogeneity cannot be explained by genetic mutations alone, and non-genetic mechanisms, including epigenetics and the tumorigenic microenvironment, were the path forward [21; 56; 59; 62; 64; 65; 66; 67].

Epigenetic Factors

Broadly speaking, epigenetic changes influence gene expression, without altering the DNA sequence, through modifications of DNA or chromatin structures [4]. In PDAC, these include: DNA methylation and non-coding RNAs (ncRNAs).

Gene expression in PDAC can be silenced through non-mutational inactivation by aberrant promoter methylation, including the driver gene *p16/CDKN2A* [49]. Aberrant ncRNA expression plays a considerable role in initiation, proliferation, and chemo-resistance of PDAC. Oncogenic microRNA-21 promotes both cell proliferation and apoptosis and targets negative regulators of *KRAS*, which further enhances signaling by this oncogene [50; 54].

Pancreatic Tumor Microenvironment

Pancreatic cancer tissue is comprised of PDAC cells and dense fibrotic stromal (stellate) cells. The stroma consists of extracellular matrix and non-neoplastic (e.g., fibroblastic, vascular, immune) cells [3]. Also described as PDAC fibrosis, the stroma makes up most of the tumor mass. Its importance beyond a physical barrier to drug penetration was not historically considered. Recognized only recently, the entire neoplastic tissue, both tumor cells and stroma, create a pancreatic tumor microenvironment that crucially facilitates PDAC growth, survival, and treatment failure [21; 51; 68].

Pancreatic cancer progresses in tandem with a stromal reaction, characterized by extensive deposition of extracellular matrix, recruitment and activation of cancer-associated fibroblasts, and high interstitial fluid pressures that compress blood vessels, causing hypoperfusion, hypovascularity, and hypoxia [21; 69]. Extracellular matrix remodeling biomechanically induces intracellular signaling and tumor-stellate cell crosstalk. PDAC cells signal to stellate cells and recruit macrophages and immune suppressor cells. In turn, stellate cells secrete factors that promote PDAC cell proliferation and migration and suppress apoptosis [51]. Biochemical activation of signaling pathways that regulate PDAC cell survival and metastasis promotes tumor growth, immunosuppression, disease progression, epithelial-mesenchymal transition (a key step of the metastatic cascade) and invasive potential, and chemotherapy resistance [3; 21; 69].

Exosomes (a macromolecule involved in RNA degradation) released by PDAC cells accumulate in other tissues to create a premetastatic niche by activating stellate cells and inducing remodeling of the host extracellular matrix, which facilitates cancer cell invasion and growth [59; 69].

HEREDITARY PDAC

In addition to the somatic mutations driving pancreatic tumorigenesis in all PDACs, specific germline variants also contribute to PDAC in some patients [48]. In many of these germline mutations, the oncogenic mechanism involves inactivation of DNA damage repair genes [49].

There are two broad categories of inherited risk for PDAC [26; 70; 71]:

- Genetic predisposition or hereditary pancreatic cancer: Germline mutations in PDAC susceptibility genes are present.
- Familial pancreatic cancer: Familial clustering of PDAC (i.e., at least one pair of affected first-degree relatives) without known germline mutations

Sporadic PDAC is when both factors are absent. However, mutations in known pancreatic cancer susceptibility genes are found in 5% to 10% of patients with apparently sporadic pancreatic cancer.

PANCREATIC CANCER SUSCEPTIBILITY SYNDROMES AND MUTATIONS	
Category	**Specific Syndromes and Germline Mutations**
Gastrointestinal tract cancers	Lynch syndrome, also termed hereditary nonpolyposis colorectal cancer (*MLH1*, *MSH2*, *MSH6*, *PMS2*) Peutz-Jeghers syndrome (*STK11/LKB1*) Familial adenomatous polyposis (*APC*)
Solid tumor cancers	Hereditary breast/ovarian syndrome (*BRCA1/2*, *PALB2*) Familial atypical multiple mole melanoma syndrome (*CDKN2A*) Li-Fraumeni syndrome (*TP53*)
Chronic pancreatitis-associated syndromes	Hereditary pancreatitis (*PRSS1*, *SPINK1*) Cystic fibrosis (*CFTR*)
Neurodegenerative disease	Ataxia-telangiectasia (*ATM*)
Source: [48; 54]	*Table 3*

PANCREATIC CANCER RISK IN PREDISPOSITION AND INHERITED CANCER SYNDROMES				
Syndrome	**Gene(s)**	**Risk of PDAC**		**Other Cancers**
		Relative	**Lifetime**	
General population	–	1	0.5%	–
Hereditary breast/ovarian cancer	*BRCA1*	2 to 3	1.2% to 2%	Breast, ovarian, prostate
	BRCA2	3.5 to 10	2% to 10%	
	PALB2	15	5% to 10%	
Familial atypical multiple mole melanoma	*CKDN2A*	13 to 36	10% to 30%	Melanoma
Peutz-Jeghers	*STK11*	75 to 125	11% to 66%	GI, lung, breast, reproductive
Hereditary nonpolyposis colon cancer (Lynch II)	*MLH1, MSH2, MSH6*	8 to 10	3.7% to 10%	Colorectal, ovary, uterine, upper GI, urinary tract
Li-Fraumeni	*TP53*	7	unknown	Breast, brain, adrenal
Familial adenomatous polyposis	*APC*	4.5	Less than 5%	Colon, upper GI, thyroid, brain
Ataxia telangiectasia	*ATM*	8 to 9	1% to 5%	Breast, prostate
Hereditary pancreatitis	*PRSS1, SPINK1*	50 to 82	25% to 44%	–
Cystic fibrosis	*CFTR*	5	Less than 5%	–
Familial pancreatic cancer[a]	1 first-degree relative	4.6	–	–
	2 first-degree relatives	6.4	–	–
	3 first-degree relatives	32	–	–
[a]Risk determined by number of affected first-degree relatives rather than specific gene.				
Source: [49; 54; 70; 73]				*Table 4*

Inherited Cancer Susceptibility Syndromes and Germline Mutations

Several genetic syndromes are associated with specific genetic alterations with an increased risk for pancreatic cancer (***Table 3***) [48; 54]. Germline mutations in familial atypical multiple mole melanoma syndrome (*CDKN2A*) and Li-Fraumeni syndrome (*TP53*) are core gene drivers in sporadic PDAC. Peutz-Jeghers syndrome is caused by germline inactivation of *STK11*, a tumor suppressor gene. Somatic *STK11* mutations are observed in approximately 4% of pancreatic cancers, suggesting *STK11* inactivation plays a role in both sporadic and familial forms [49].

Familial Pancreatic Cancer

An estimated 10% to 15% of all pancreatic cancers are attributable to genetic causes. Pancreatic cancer aggregates in some families; 5% to 10% of individuals with pancreatic cancer have a family history of the disease [26; 70; 72]. Familial pancreatic cancer represents 90% of all hereditary PDAC cases. The relative risk of PDAC increases with the number of affected first-degree relatives.

A specific gene defect responsible for familial pancreatic cancer has not been identified, but a rare autosomal-dominant gene may be responsible, putting 0.4% to 0.7% of the population at risk for developing PDAC [26; 70; 72]. Details about the relative and lifetime risks of PDAC, and the other prevalent cancers associated with specific germline mutations in cancer susceptibility syndromes and familial pancreatic cancer, are summarized in ***Table 4***.

PANCREATIC CANCER SCREENING

With the low population incidence of PDAC (lifetime risk: 1.3%), absence of biomarker screening targets, and high cost of sensitive imaging methods, the U.S. Preventive Services Task Force recommended against screening for pancreatic cancer in asymptomatic adults in 2019, reaffirming its previous conclusion in 2004 [74]. As population screening to achieve earlier detection and intervention of PDAC is not currently feasible, other approaches for this objective have been identified.

In Australia, public awareness campaigns have highlighted the often vague symptoms of PDAC and encouraged individuals to seek medical attention early. Underscoring this point, one study found that many people who were ultimately diagnosed with PDAC were falsely reassured by the subtle, intermittent nature of their symptoms over the preceding months [75; 76].

As a relatively rare cancer, many primary care providers will only see a PDAC case every few years, making it imperative to elevate awareness of early PDAC signs and symptoms among these professionals. A retrospective case-control study in primary care found that patients sought medical attention 18 times on average in the period preceding their pancreatic cancer diagnosis. PDAC was associated with 11 alarm symptoms; back pain, lethargy, and new-onset diabetes were unique features of PDAC [75; 77].

Specific screening efforts in PDAC have focused on identifying high-risk individuals [48]. In 2020, the International Cancer of the Pancreas Screening (CAPS) Consortium updated its consensus recommendations for the management of individuals with increased risk of pancreatic cancer based on family history or germline mutation status [71]. For selected high-risk individuals, pancreatic surveillance is recommended to detect and resect early pancreatic cancer and its high-grade precursors (***Table 5***). No consensus was reached on whether surveillance should be performed for hereditary pancreatitis.

However, it is important to remember that among patients with PDAC unselected for their family history of pancreatic cancer who had a germline susceptibility gene mutation, only 10% of these patients had a family history of pancreatic cancer, and most did not have a cancer family history to suggest an inherited cancer syndrome. Because family history remains one of the best predictors of future pancreatic cancer risk, routine gene testing of patients with newly diagnosed PDAC and their families may yield significant clinical benefits [78].

Genetic counseling of patients before and after any genetic testing is essential, to provide understanding and reassurance and to avoid harm. A challenge to less restrictive testing of patients with new PDAC is there are not enough genetic counselors to provide this service; this shortage of expertise applies to other cancers as well [78].

GERMLINE AND SOMATIC TESTING AND MOLECULAR ANALYSIS

When should patients with pancreatic cancer have germline testing and gene profiling offered?

With strong consensus that benefits outweigh harms, in 2018 the ASCO recommended germline genetic testing for patients with PDAC, even if family history is unremarkable, if an informative result could directly benefit the patient or their family members [73]. This stance was adopted in 2020 by the NCCN. Consensus has subsequently expanded.

All patients with pancreatic cancer should have germline testing and gene profiling offered as quickly as possible after diagnosis; the implications for first-line therapy and beyond are significant [79; 80]. The 2020–2021 ASCO and NCCN recommendations are for all patients with PDAC to receive germline genomic testing using comprehensive gene panels for hereditary cancer syndromes, and targeted (somatic) profiling of tumor tissue using next-generation sequencing [10; 11]. Patients with locally advanced or metastatic PDAC should have available tumor tissue tested for DNA mismatch repair deficiency (dMMR) and microsatellite instability – high (MSI-H) status. It is also recommended that these patients undergo testing for actionable somatic mutations, including fusions (*ALK*, *NRG1*, *NTRK*, *ROS1*), mutations (*BRAF*, *BRCA1/2*, *HER2*, *KRAS*, *PALB2*), and mismatch repair deficiency (dMMR).

INTERNATIONAL CANCER OF THE PANCREAS SCREENING (CAPS) CONSORTIUM CONSENSUS ON SCREENING FOR PANCREATIC CANCER IN PATIENTS WITH INCREASED RISK FOR FAMILIAL PANCREATIC CANCER

What is the goal of pancreatic surveillance?

The primary goal is to prevent the emergence of and death from pancreatic cancer by identifying and treating stage I pancreatic cancer (resected with negative margins) and pancreatic cancer precursor lesions with high-grade dysplasia (PanIN or IPMN).

Who should be screened?

All patients with Peutz-Jeghers syndrome (carriers of a germline *LKB1/STK11* mutation)

All carriers of a germline *CDKN2A*(p16) mutation

Carriers of a germline *BRCA2*, *BRCA1*, *PALB2*, *ATM*, *MLH1*, *MSH2*, or *MSH6* gene mutation with at least one affected first-degree relative

Individuals with at least one first-degree relative with pancreatic cancer who in turn also has a first-degree relative with pancreatic cancer (familial pancreatic cancer kindred)

At what age[a] should pancreatic surveillance begin?

Familial pancreatic cancer kindred	Start at 50 or 55 years of age, or 10 years younger than the youngest affected blood relative
Mutation carriers	For *CDKN2A* and Peutz-Jeghers syndrome, start at 40 years of age
	For *BRCA2*, *ATM*, *PALB2*, *BRCA1*, and *MLH1/MSH2*, start at 45 or 50 years of age, or 10 years younger than the youngest affected first-degree relative

What tests and indications?

Indication	Interval	Test(s)
Routine	At baseline and during follow-up	MRI/MRCP and endoscopic ultrasound Fasting blood glucose and/or HbA1c
Concerning abnormalities for which immediate surgery is not indicated	After 3 to 6 months	Repeat follow-up testing
No abnormalities or only non-concerning abnormalities (e.g., pancreatic cysts without worrisome features)	After 12 months	Repeat follow-up testing
If concerning features on imaging	Upon indication	Serum CA 19-9
Solid lesions of ≥ 5 mm Cystic lesions with worrisome features Asymptomatic main pancreatic duct strictures (with or without mass)	Upon indication	Endoscopic ultrasound-guided FNA
Solid lesions, regardless of size Asymptomatic main pancreatic duct strictures of unknown etiology (without mass)	Upon indication	CT
Positive FNA and/or a high suspicion of malignancy on imaging	Upon indication	Surgery[b]

[a]Age to initiate surveillance depends on gene mutation status and family history. There is no consensus on the age to end surveillance.

[b]When surgery is indicated, it should be oncologic radical resection at a specialty center.

CA 19-9 = carbohydrate antigen 19-9; CT = computed tomography; FNA = fine-needle aspiration; HbA1c = hemoglobin A1c; IPMN = intraductal papillary mucinous neoplasm; MRI/MRCP = magnetic resonance imaging/magnetic retrograde cholangiopancreatography = PanIN: pancreatic intraepithelial neoplasia.

Source: [70; 71] *Table 5*

CLINICAL EVALUATION OF PANCREATIC CANCER

Most pancreatic cancers (approximately 75%) originate in the head of the pancreas and typically metastasize to regional lymph nodes first, then to the liver. PDAC can also directly invade surrounding visceral organs (e.g., duodenum, stomach, colon); metastasize to any surface in the abdominal cavity via peritoneal spread where development of ascites carries an ominous prognosis; or spread to the skin as painful nodular metastases. By the time of diagnosis, 85% to 90% of patients have locally advanced tumors that have involved retroperitoneal structures, spread to regional lymph nodes, or metastasized to the liver or lung [2; 13; 24; 81].

Early-stage pancreatic cancer is notoriously difficult to diagnose. The most common symptoms in a series of patients diagnosed with PDAC were fatigue (86%), weight loss (85%), anorexia (83%), abdominal pain (79%), epigastric pain (71%), jaundice (56%), nausea (51%), diarrhea (44%), pruritus (32%), and steatorrhea (25%) [82].

Abdominal pain, jaundice, and weight loss are nonspecific, subtle in onset, and easily attributed to other processes. Unless the healthcare provider has a high index of suspicion for the possibility of underlying pancreatic carcinoma, this can make it difficult to know when to escalate a workup, as PDAC lacks a specified diagnostic algorithm [2; 24].

Development of abdominal pain, jaundice, or weight loss in the context of newly diagnosed diabetes, family history of PDAC, or history of pancreatitis should trigger inclusion of PDAC in the differential diagnosis [2]. Furthermore, past three-year onset of diabetes or ongoing hyperglycemia with significant weight loss and decreasing serum lipids should be considered a potential PDAC, even if abdominal pain or jaundice are absent, with urgent referral a priority.

As noted, pancreatic cancer-associated diabetes and pancreatic cancer cachexia are distinct paraneoplastic syndromes with clinical parameters that may alert attentive clinicians to pursue an appropriately aggressive workup [47]. The lethality of pancreatic cancer merits such an approach despite the absence of formal diagnostic guidelines in this area.

NEUROPSYCHIATRIC SYMPTOMS AND PANCREATIC CANCER

Depression is reported to be more common in patients with pancreatic cancer than with other abdominal tumors. In some patients, depression may be the most prominent presenting symptom, possibly secondary to delayed diagnosis. In addition, although patients may not communicate it to their families, they are often aware that a serious illness of some kind is occurring in them [24]. The risk of suicide among male patients with PDAC is almost 11 times higher than the general male population. Patients who underwent resection are more likely to commit suicide, specifically in the early postoperative period [83].

The association between mood disorders, fatigue, and PDAC has been assumed secondary to the psychosocial impact of diagnosis, loss of independence, and treatment toxicity [2]. However, it is now clear that PDAC has independent detrimental effects on the brain. These symptoms, often present before a diagnosis, are collectively the greatest drivers of declines in health-related quality of life and are independently predictive of survival. Evidence points to neuroinflammatory processes and the need to rethink PDAC as a systemic disease [2].

FAMILY HISTORY

The importance is emphasized of taking a thorough family history when seeing a new patient with pancreatic cancer. A family history of pancreatitis, melanoma, and pancreatic, colorectal, breast and ovarian cancers should be noted [11].

If a cancer syndrome is identified, at-risk relatives should be offered genetic counseling. With or without a known syndrome, individuals with a suspicious family history should be advised on risk-reducing strategies, including smoking cessation and weight loss. The possibility of screening for pancreatic and other cancers should be discussed.

Referral for genetic counseling should be considered for patients diagnosed with pancreatic cancer, especially those with a family history of cancer or who are young, those of Ashkenazi Jewish ancestry, or for whom a hereditary cancer syndrome is suspect. A free pancreatic cancer risk prediction tool, PancPRO, is available and may help determine risk [11].

COMMON PRESENTING SYMPTOMS AND SIGNS

Some, but not all, initial symptoms of PDAC result from a mass effect, such that pancreatic tumor location influences the stage of disease progression when symptoms appear [13].

Abdominal Pain

What are the most common signs/symptoms in patients with pancreatic cancer?

Abdominal pain is the most common symptom, usually insidious in onset and often present for one to two months at the time of presentation, the pain is often severe, and unrelenting in nature. The typical gnawing, visceral quality of pain is generally epigastric, radiating to the sides and/or straight through to the back; some patients may describe the pain as originating in the back. Nighttime pain is often the predominant complaint. Some patients note increased pain after eating and worsened pain when lying flat [24; 81]. Rarely, acute pain develops when an episode of acute pancreatitis results in tumor occlusion of the main pancreatic duct [84].

While roughly one-third of patients may not have pain at the time of initial presentation, all patients will develop pain at some point [24]. Pancreatic cancer is one of the most painful malignancies, and effective pain control is extremely important [85]. This issue will be discussed in detail later in this course.

Jaundice

The most characteristic sign of tumor in the pancreatic head is obstructive jaundice, for which patients may seek medical attention before their tumor grows large enough to cause abdominal pain (and thus, a somewhat better prognosis). These patients usually notice a darkening of their urine and/or lightening of their stools before they or their families notice the change in skin pigmentation. Jaundice secondary to a tumor in the body or tail of the pancreas typically occurs at a later stage and may be secondary to liver metastases of PDAC [2; 84].

Pruritus can accompany and often precedes obstructive jaundice. If present, it is often the patient's most distressing symptom [24].

Significant Weight Loss

A characteristic feature of pancreatic cancer, significant weight loss may be related to cancer-associated anorexia and/or subclinical malabsorption from pancreatic exocrine insufficiency caused by pancreatic duct obstruction. Nausea and early satiety from gastric outlet obstruction and delayed gastric emptying from the tumor can contribute to weight loss [24]. Significant weight loss is a symptom of cachexia.

Cachexia

Pancreatic cancer cachexia is a multifactorial paraneoplastic syndrome characterized by a loss of skeletal muscle mass, commonly associated with adipose tissue wasting and anorexia, fatigue, and reduced exercise tolerance. Cachexia develops in approximately 80% of patients with PDAC, in whom the syndrome is typically present at diagnosis and responds poorly to therapeutic interventions [47; 86].

Pancreatic cancer leads to the development of cachexia through a combination of distinct factors that explain its high prevalence and clinical importance in this disease [86]:

- Systemic factors, including metabolic changes and pathogenic signals related to PDAC tumor biology
- Factors resulting from the disruption of the digestive and endocrine functions of the pancreas
- Factors related to the close anatomic and functional connection of the pancreas with the gut

Additional Symptoms

The initial assessment can uncover additional diagnostic clues. Undiagnosed diabetes leads to symptoms of glucose intolerance (e.g., polyuria, polydipsia). PDAC can interfere with production of digestive enzymes by the pancreas (pancreatic exocrine insufficiency) and with the ability to break down food and absorb nutrients (malabsorption) in some patients. This malabsorption causes bloating, gas, and a watery, greasy, and/or foul-smelling diarrhea, leading to weight loss and vitamin deficiencies [81].

While long-standing diabetes is a risk factor for later development of PDAC, new-onset hyperglycemia or diabetes has been identified in the majority of patients at diagnosis of otherwise asymptomatic PDAC. Deregulation in glucose homeostasis is often accompanied by changes in subcutaneous adipose tissue. Both represent paraneoplastic syndromes caused by the underlying PDAC [2].

This research is among the most important knowledge advances in PDAC in the past decade. In addition to metabolic deregulation, the pre-diagnostic soft tissue changes and symptoms of cachexia have profound implications for screening, early diagnosis, treatment selection, and patient prognosis [2].

Tumors can also grow locally into the duodenum (proximal for the head of the pancreas, distal for the body and tail of the pancreas) and result in an upper gastroduodenal obstruction [13]. Tumor in the body or tail of the pancreas may cause splenic vein obstruction, resulting in splenomegaly, gastric and esophageal varices, and gastrointestinal hemorrhage [81].

PHYSICAL EXAMINATION

Clinical signs of PDAC during physical examination include jaundice, pruritus, steatorrhea, and vascular issues [2; 24; 82; 84]. Healthcare professionals can usually recognize clinical jaundice when total bilirubin reaches 2.5–3 mg/dL. Patients and their families do not usually notice clinical jaundice until total bilirubin reaches 6–8 mg/dL. Patients with jaundice may have a palpable gallbladder (i.e., Courvoisier sign). As noted, patients with clinical jaundice may have skin excoriations from unrelenting pruritus. If the pancreas has lost the ability to secrete fat-digesting enzymes or if the main pancreatic duct is blocked, steatorrhea will develop.

Migratory thrombophlebitis (i.e., Trousseau syndrome) and venous thrombosis may be present, reflecting the hypercoagulable state that frequently accompanies pancreatic cancer. Thromboembolic events (both venous and arterial) are especially prevalent in advanced disease, and thromboembolic complications occur more commonly with tumors in the pancreatic tail or body.

Multiple arterial emboli resulting from nonbacterial thrombotic endocarditis may be the presenting sign of PDAC. Marantic endocarditis (also known as nonbacterial thrombotic endocarditis) may develop in patients with pancreatic cancer and possibly mimic subacute bacterial endocarditis.

METASTATIC DISEASE

Metastatic disease most commonly affects the liver, peritoneum, lungs, and less frequently, bone [24; 84]. Patients presenting with or developing advanced intra-abdominal disease may have ascites, a palpable abdominal mass, hepatomegaly from liver metastases, or splenomegaly from portal vein obstruction. Subcutaneous metastases (termed Sister Mary Joseph nodules) in the paraumbilical area signify advanced disease; pancreatic cancer is the origin of a cutaneous metastasis to the umbilicus in 7% to 9% of cases [24; 84]. A metastatic mass in the rectal pouch may be palpable on rectal examination (Blumer shelf). As a metastatic node, left supraclavicular lymphadenopathy may be palpable, while other nodes in the cervical area may also be involved.

LABORATORY TESTING

Routine laboratory tests are often abnormal but nonspecific for PDAC. Common abnormalities include an elevated serum bilirubin and alkaline phosphatase levels, and presence of mild anemia [84].

Patients presenting with jaundice or epigastric pain should be evaluated with complete blood count, blood chemistry panel, and liver function tests to help assess the extent of cholestasis (bilirubin), liver metastasis (alkaline phosphatase), hepatitis (aminotransferases), and nutritional status (albumin, prealbumin). With epigastric pain, serum lipase should be measured to evaluate for acute pancreatitis [2].

DIFFERENTIAL DIAGNOSIS

Differential diagnosis before imaging and biopsy includes acute/chronic pancreatitis, cholangitis, cholecystitis, choledochal cyst, peptic ulcer disease, cholangiocarcinoma, and gastric cancer [85]. Unlike pancreatic exocrine tumors, the symptoms of pancreatic neuroendocrine tumors are distinctly related to excessive secretion of hormones such as insulin, glucagon, gastrin, somatostatin, and vasoactive peptide, resulting in hypoglycemia, hyperglycemia, and GI disturbances such as peptic ulcer and diarrhea.

THE DIAGNOSTIC AND STAGING WORKUP

It is not possible to reliably diagnose a patient with pancreatic cancer based on symptoms and signs alone. Abdominal imaging is used in the diagnostic and staging workup of a patient with suspected PDAC. Additional testing is based on the initial findings, the patient's clinical presentation and risk factors [2].

Accurate PDAC detection and staging at the time of presentation carries substantial implications for appropriate recommendation to patients of the most suitable treatment option, thus maximizing the survival benefit for patients in whom complete resection can be achieved and minimizing the morbidity from unnecessary laparotomy or major surgery in patients with high risk of residual disease following resection. The accuracy critically depends on the appropriate imaging protocol and radiologist experience [2; 87]. As such, decisions about diagnosis, resectability, and management of pancreatic cancer should involve multidisciplinary consultation at high-volume centers [11].

IMAGING

Multidetector Computed Tomography

What is the preferred imaging for initial evaluation of suspected PDAC?

Multidetector computed tomography (MDCT) angiography with intravenous (IV) contrast is the preferred imaging for initial evaluation of suspected PDAC. The Pancreatic CT Protocol standardizes its use, making MDCT highly accurate for assessing tumor extent, vascular invasion, and distant metastases [11; 16; 88; 89]. The NCCN recommends that MDCT angiography should also cover the chest and pelvis for complete staging [11].

The American Society of Clinical Oncology recommends a multiphase computed tomography (CT) scan of the abdomen and pelvis using a pancreatic protocol or magnetic resonance imaging (MRI) be performed for all patients with pancreatic cancer to assess the anatomic relationships of the primary tumor and to assess for the presence of intra-abdominal metastases.

(https://ascopubs.org/doi/10.1200/JCO.19.00946. Last accessed August 19, 2021.)

Strength of Recommendation/Level of Evidence: Strong/high

MDCT is 77% accurate in predicting resectability and 93% accurate in predicting unresectability [85]. MDCT may be superior to magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) in vascular enhancement of a PDAC, the most important parameter of resectability. However, MDCT is inferior to MRI/MRCP in depicting isodense tumors or tumors smaller than 1.5 cm in size [54].

Magnetic Resonance Imaging/Magnetic Resonance Cholangiopancreatography (MRI/MRCP)

Abdominal MRI/MRCP with IV contrast also employs a standard multiphase protocol in PDAC, with efficacy comparable to MDCT in preoperative evaluation and assessment of vascular invasion. The sensitivity of MRI/MRCP in detecting liver metastases is nearly 100% (vs. 80% with MDCT) [81; 85].

Selection of initial MDCT or MRI/MRCP is typically based on local availability and expertise [81; 85]. Following initial MDCT, MRI/MRCP is used when PDAC is highly suspected but negative on MDCT, for characterizing small or indeterminate pancreatic and hepatic tumors, and in patients with severe allergy to iodinated IV contrast material used in MDCT [54; 81; 85].

Endoscopic Retrograde Cholangiopancreatography (ERCP)

With endoscopic retrograde cholangiopancreatography (ERCP), contrast dye is injected into the biliary ducts and pancreatic duct with an endoscope, and the level of obstruction is delineated. In some case, placement of a biliary stent can help relieve symptoms of jaundice [85]. Patients with obstructive jaundice may have ERCP as the first diagnostic procedure [81].

Ultrasonography

Transabdominal ultrasonography is useful in initial screening of patients who present with possible obstructive jaundice and can rapidly and accurately assess for biliary obstruction. However, definitive diagnosis requires other imaging [24].

Endoscopic ultrasonography is superior to MDCT in detecting solid pancreatic lesions less than 2 cm in size, with accuracy of about 92% [54]. Endoscopic ultrasonography-guided fine-needle aspiration (FNA) also allows for tissue sampling at the time of endoscopic ultrasonography diagnosis [24].

With the restricted field of view, endoscopic ultrasonography is complimentary to MDCT, but it should be used before other imaging options if no pancreatic mass is evident on MDCT. Endoscopic ultrasonography is also valuable in detecting tumor involvement of blood vessels or lymph nodes [11; 89].

Positron-Emission Tomography (PET)

Positron-emission tomography (PET) imaging alone does not offer added advantages to MDCT. Combining PET with CT (PET/CT) is a more recent development that may enhance the detection of occult metastases in pancreatic cancer. The NCCN guidelines consider PET/CT an evolving technology; its role in the diagnosis of PDAC is not yet established [11].

BIOPSY

A positive biopsy is not needed in patients with resectable PDAC before undergoing surgery; biopsy may result in seeding, interfere with definitive surgery, and needlessly delay surgical resection if nondiagnostic [11]. However, histologic confirmation of a pancreatic cancer diagnosis is required in some situations, and endoscopic ultrasonography-guided FNA biopsy is the best modality for obtaining a tissue diagnosis [84].

A pathologic diagnosis is indicated to confirm PDAC in locally advanced or metastatic disease, before neoadjuvant therapy, and in atypical presentations in which differential diagnosis is needed with other pancreatic masses (e.g., pancreatitis, lymphoma, tuberculosis). If a biopsy does not confirm malignancy, it should be repeated at least once [16].

The difficulty of diagnosing PDAC in patients with underlying chronic pancreatitis is noteworthy. In such cases, all typical imaging methods may show abnormalities that do not differentiate between PDAC and chronic pancreatitis, and carbohydrate antigen 19-9 (CA19-9) may be similarly elevated in pancreatitis. These patients may require combined multiple imaging modalities, close follow-up, serial imaging studies, and in some cases, empiric resection to diagnose an underlying pancreatic carcinoma [24].

CARBOHYDRATE ANTIGEN 19-9 (CA19-9)

CA19-9 is a sialylated Lewis A blood group antigen, commonly expressed and shed in benign and malignant pancreatic and biliary disease. Although unsuitable for asymptomatic screening, CA19-9 is the most clinically useful biomarker in PDAC, with good sensitivity (79% to 81%) and specificity (82% to 90%) in symptomatic patients. A normal serum level is 37 U/mL [90].

Preoperative CA19-9 provides important prognostic information. Levels <100 U/mL imply likely resectable disease, while levels >100 U/mL suggest unresectablity or metastatic disease. Fewer than 4% of patients with levels >300 U/mL have resectable tumors [24; 90].

In one study, patients with preoperative CA19-9 levels <37 U/mL showed longer median survival (22 to 40 months) than patients with levels >37 U/mL (7 to 30 months). Post-treatment changes (two to five weeks post-resection; six to eight weeks post-chemotherapy) from baseline may predict overall survival [90; 91].

Post-operative CA19-9 levels of <37 U/mL, <200 U/mL, and >500 U/mL were associated with three-year survival rates of 49%, 38%, and 0%, respectively. Post-chemotherapy CA19-9 decreases of ≥20% predicted prolonged disease-free survival and overall survival [90; 91].

Limitations

Around 5% to 10% of the population lacks the enzyme necessary to produce CA19-9; monitoring pancreatic cancer with this marker will not be possible in these individuals [24]. Biliary obstruction also stimulates the secretion of CA19-9. Hyperbilirubinemia is associated with elevated CA19-9 and false positivity in patients with obstructive jaundice. Following the treatment of obstruction, re-evaluation of CA19-9 should improve its diagnostic utility [92].

The NCCN recommends measurement of serum CA19-9 levels after neoadjuvant treatment, prior to and immediately following surgery before adjuvant therapy, and in surveillance. The importance is stressed of obtaining CA19-9 immediately before a therapeutic intervention to have an accurate baseline from which to follow response [11].

THE STAGING WORKUP

When a mass lesion of the pancreas is detected on MDCT (with or without additional imaging), it is reasonable to conclude that a neoplasm is present and is most likely malignant PDAC. After a probable diagnosis of pancreatic cancer is made, the next step is the staging evaluation to establish disease extent and resectability. Unlike many other cancers, imaging is the primary means through which the stage of pancreatic cancer is determined [11].

Using initial MDCT (with or without additional imaging), two different systems are involved [11; 93]:

- American Joint Committee on Cancer (AJCC) TNM staging system, to assess tumor status/extent (T), lymph nodes (N), and metastasis (M)
- NCCN guideline to characterize resectable, borderline resectable, or locally advanced disease

TNM Staging

The AJCC system (***Table 6***) is used for staging PDAC in two contexts [16; 94]:

- Clinical staging of all patients with imaging assessment of tumor size and extension, nodal involvement, and distant disease spread
- Pathologic staging of tissue specimens obtained during resection for presence of viable tumor cells

Clinical staging identifies the primary tumor and its vessel involvement, enlarged or suspicious lymph nodes, and metastatic disease sites. TNM staging provides important prognostic information (***Table 7***), but does not assess whether the PDAC tumor is amenable to surgical resection [54; 94].

Resectability Assessment

Complete resection is the only potentially curative treatment for PDAC, but fewer than 20% of patients presenting with PDAC have localized and easily resectable tumors, and non-curative resections provide no survival benefit. Thus, accurate assessment of resectability is crucial [24; 87; 89].

The NCCN guideline classes PDAC resectability into the following clinical stages [11]:

- Stage 1: Resectable
- Stage 2: Borderline resectable (i.e., tumors that are involved with nearby structures so as to be neither clearly resectable nor clearly unresectable with a high chance of removal of all macroscopic disease)
- Stage 3: Locally advanced (i.e., tumors that are involved with nearby structures to an extent that renders them unresectable despite the absence of metastatic disease)
- Stage 4: Metastatic (i.e., non-resectable)

Localized PDAC falls on a spectrum from high to low resectability, determined by the extent of vessel contact and whether the involvement is arterial or venous (***Figure 1***) [11; 54; 84; 87; 89; 95]. Major peripancreatic vessels include the superior mesenteric vein and artery, portal vein, common hepatic artery, and celiac artery. Tumor contact can be characterized as encasement (≥180 degrees of the vessel circumference), abutment (<180 degrees of the circumference), or direct involvement (absence of fat plane between tumor and vessel).

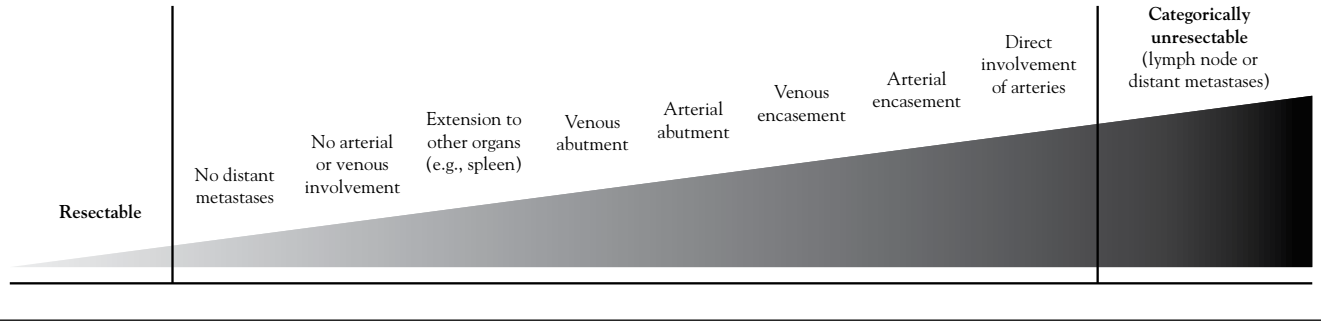
In the past, vascular infiltration by PDAC was considered unresectable, but surgical advances have increased the number of patients with initial borderline resectable or locally advanced disease who can undergo resection. In general, venous abutment or encasement is usually borderline resectable as long as the venous segment is reconstructable. Arterial reconstruction is substantially more difficult and risky than venous reconstruction with comparable tumor contact.

Based on PDAC clinical status of resectable, borderline resectable, locally advanced, or metastatic disease, additional considerations and therapeutic approaches will be undertaken. The time-urgency between the first availability of full imaging findings, multidisciplinary evaluation, the diagnostic and staging workup, discussion with the patient of available treatment options, and treatment initiation cannot be overstated in this aggressive malignancy.

AMERICAN JOINT COMMISSION ON CANCER EXOCRINE PANCREATIC CANCER TNM STAGING	
Category	**Criteria**
Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ, including high-grade PanIN (PanIN-3) and IPMN, ITPN, or MCN with high-grade dysplasia
T1	Tumor ≤2 cm in greatest dimension
T1a	Tumor ≤0.5 cm in greatest dimension
T1b	Tumor >0.5 and <1 cm in greatest dimension
T1c	Tumor 1–2 cm in greatest dimension
T2	Tumor >2 and ≤4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension
T4	Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery, regardless of size
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one to three regional lymph nodes
N2	Metastasis in four or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
IPMN = intraductal papillary mucinous neoplasm; ITPN = intraductal tubulopapillary neoplasm; MCN = mucinous cystic neoplasm; PanIN = pancreatic intraepithelial neoplasia	
Source: [93]	*Table 6*

AMERICAN JOINT COMMISSION ON CANCER ANATOMIC STAGE/ PROGNOSTIC GROUPS FOR EXOCRINE PANCREATIC CANCER			
Stage	**T**	**N**	**M**
A	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1–T3	N1	M0
III	Any T	N2	M0
	T4	Any N	M0
IV	Any T	Any N	M1
Source: [93]			*Table 7*

SPECTRUM OF PANCREATIC CANCER RESECTABILITY



Source: [84; 89; 95] *Figure 1*

TREATMENT APPROACHES FOR PANCREATIC CANCER

As mentioned, the initial imaging workup of PDAC confirms the diagnosis, searches for evidence of metastases, and classifies nonmetastatic PDAC into resectable, borderline resectable, or locally advanced disease based on the involvement of surrounding arterial (superior mesenteric artery, common hepatic artery, and celiac axis) and venous (superior mesenteric vein or portal vein) structures, and other nearby organs and lymph nodes [96].

On average, 10% to 20% of patients initially present with "up-front" resectable PDAC. However, an increasing number of patients with initial borderline resectable or locally advanced disease are eligible for surgical resection as a result of neoadjuvant (i.e., before resection) therapies which may downstage the tumor, and advances in surgical technique, such as venous reconstruction in a vascular infiltration formerly considered unresectable [2].

In all therapeutic decisions, multidisciplinary collaboration to formulate treatment planning and disease management that incorporates patient preferences and available support, their comorbidity profile, symptom burden, and performance status should be the standard of care [6; 7; 10].

PATIENT FUNCTIONAL STATUS

Performance status is an important indicator of general well-being and the ability to perform activities of daily living in patients with cancer and is frequently assessed in both clinical and research settings. Performance status is repeatedly shown to predict important clinical outcomes, including quality of life, chemotherapy toxicity, response to chemotherapy, terminal illness, progression-free survival, and overall survival in patients with cancer [97].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the ASCO, the baseline performance status, symptom burden, and comorbidity profile of a person diagnosed with potentially curable pancreatic cancer should be carefully evaluated.

(https://ascopubs.org/doi/10.1200/JCO.19.00946. Last accessed August 19, 2021.)

Strength of Recommendation/Level of Evidence: Strong/high

The Karnofsky Performance Status tool has been used for this purpose, but PDAC guidelines and randomized controlled trials now solely employ the Eastern Cooperative Oncology Group Performance Status (ECOG) scale (***Table 8***) [97]. For instance, some chemotherapies are indicated solely for patients with good ECOG performance status (0 or 1).

Baseline functional status and comorbidity profile should be carefully evaluated, because both have major implications for a person's ability to tolerate therapy. Performance status is consistently identified as a prognostic factor for people with pancreatic cancer. It is also an important determinant in treatment selection; some patients with up-front resectable PDAC may be physically weakened by weight loss and cachexia to an extent that places them at high risk of serious complications or mortality from definitive surgery. Performance status also helps predict chemotherapy toxicity, which can determine the treatment approach for patients with performance status 0 to 1 (multi-agent regimens) or performance status ≥2 (e.g., single-agent gemcitabine) [8].

EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS SCALE	
Score	**Definition**
0	Fully active No performance restrictions
1	Strenuous physical activity restricted Fully ambulatory and able to carry out light work
2	Capable of all self-care but unable to carry out any work activities Up and about >50% of waking hours
3	Capable of only limited self-care Confined to bed or chair >50% of waking hours
4	Completely disabled Cannot carry out any self-care Totally confined to bed or chair
5	Deceased
Source: [98]	*Table 8*

Similarly, the comorbidity profile can influence the choice of chemotherapy, such as avoiding fluoropyrimidine-based regimens in patients with a known history of uncontrolled coronary artery disease. Nonetheless, performance status and comorbidities alone should not be used simply to rule in or out patients for treatment. For instance, disease control of comorbidities, such as controlled type 2 diabetes, can indicate that patient benefit from treatment may outweigh risks associated with poorly controlled comorbid diabetes [8].

RECOMMENDED TREATMENT OPTIONS BY CLINICAL STAGE

What is considered a curative treatment for PDAC?

Treatment approaches for PDAC include surgical resection, chemotherapy, radiation therapy, and combined regimens (chemoradiation therapy). Chemotherapy is the backbone of pancreatic cancer treatment; most patients present with disease too advanced to benefit from surgery or resection alone may be insufficient to provide a substantive survival advantage over best supportive care. Chemotherapy and radiation therapy also have a role in palliation, as will be discussed in a later section [99].

Curative surgical approaches for resectable pancreatic cancer are well-established. In contrast, the pace of new U.S. Food and Drug Administration (FDA) approvals and/or phase III evidence continue to make chemotherapy, molecular-targeted therapy, radiation, and chemoradiotherapy approaches a fluid, evolving area, requiring frequent updating and revisions in multidisciplinary clinical practice guidelines for pancreatic cancer treatment. Many potential treatment approaches lacking phase III or prospective evidence are being addressed, with publication of trial results awaited [2].

Resectable or Borderline Resectable PDAC

For patients with resectable or borderline resectable PDAC, neoadjuvant therapy consists of chemotherapy with or without radiation therapy before radical pancreatic resection [99]. Radical pancreatic resection may include Whipple procedure (pancreaticoduodenal resection) or total pancreatectomy when necessary for adequate margins. Distal pancreatectomy is indicated for tumors of the body and tail of the pancreas.

Following resection, patients may receive postoperative chemotherapy or postoperative chemoradiation therapy (typically fluorouracil [5-FU] chemotherapy and radiation therapy) [99].

Locally Advanced PDAC

Chemotherapy with or without targeted therapy is recommended for patients with locally advanced PDAC [99]. For patients without metastatic disease, this should be followed by chemoradiation therapy. If removal is a possibility, radical pancreatic resection may be attempted. Palliative surgery options include surgical biliary and/or gastric bypass, percutaneous radiologic biliary stent placement, or endoscopic biliary stent placement.

Metastatic or Recurrent PDAC

Treatment of metastatic or recurrent PDAC is limited to chemotherapy with or without targeted therapy [99]. Palliative approaches should be used whenever available and feasible to improve patient comfort and quality of life.

RESECTION OF PANCREATIC CANCER

Selecting patients for surgery should be based on the probability of cure as determined by resection margins. Other factors include comorbidities, overall performance status, and age. Pancreaticoduodenectomy and distal and total pancreatectomy are curative resection options based on the location, size, and locally invasive aspects of the tumor. Each has its own set of perioperative complications and risks, which should be considered by the surgical team and discussed with the patient [24].

Mortality rates from resection have fallen significantly, but morbidity remains common and interferes the delivery of adjuvant therapy in up to 40% of patients. The NCCN recommends that patients seek out high-volume centers performing more than 15 to 20 resections annually, with multidisciplinary expertise to optimize their treatment plan and increase opportunities for clinical trial participation [2].

The only curative treatment for PDAC is radical surgery, but potential cure is only possible with a microscopically negative resection margin (R0). Macroscopic (R2) and microscopic (R1) margin infiltration have survival trends similar to patients without surgery. R0 is a minimum >1 mm distance of viable tumor cells from the resection margin, R1 is ≤1 mm distance. A retrospective analysis of 44,852 patients with PDAC reported median survival of 19.7 months following R0, 14.3 months following R1, and 9.8 months with R2 resections compared with 10.3 months without surgery [100]. An incomplete tumor resection imposes morbidity risks without benefit to the patient, and the aim of resection is to obtain microscopically negative margins (R0) [101].

Tissue specimens obtained during resection are examined. During resection, lymphadenectomy is performed, including at least 15 lymph nodes, which are likewise examined as part of pathologic staging [16].

With surgical advances and greater use of adjuvant therapies, long-term cancer survival outcomes following resection were anticipated to improve over time [102]. However, in 1,147 pancreatic resections performed over three decades at the Memorial Sloan Kettering Cancer Center, a lack of progress in long-term survival was reported. Although patients treated between 2000 and 2009 had lower rates of operative mortality and greater one-year survival, for patients treated in the 1980s, 1990s, and 2000s, the median survival was 23.2, 25.6, and 24.5 months, respectively [103]. The five-year survival rates were 17%, 20%, and 8%, respectively. These data underscore the need for earlier detection and more effective systemic therapies [102].

Approaches

Pancreaticoduodenectomy (Whipple Procedure)

Used for tumors in the pancreatic head or periampullary region, the conventional Whipple procedure involves removal of the pancreatic head, duodenum, gallbladder, and the antrum of the stomach, with surgical drainage of the distal pancreatic duct and biliary system, usually through anastomosis to the jejunum. The primary reason for removing so much of the intra-abdominal structures is that they all share a common blood supply [24; 102].

The former high morbidity and mortality rates of Whipple have declined with the greater experience of a more limited number of surgeons who regularly perform the procedure in high-volume centers [102]. Common morbidities include delayed gastric emptying in roughly 25% of patients, which may require nasogastric decompression and a longer hospital stay. Pancreatic anastomotic leak can be treated with adequate drainage. Postoperative abscesses are not uncommon [24].

With operative mortality associated with Whipple decreasing from around 25% in the 1970s to less than 2% at high-volume centers in the 2010s, the focus has shifted from surviving the operation to surviving the cancer [104].

Distal Pancreatectomy

Distal pancreatectomy is a procedure for tumors in the pancreatic body or tail. It has a lower mortality than standard Whipple, but its use in curative resection is limited; with tumors in this location seldom causing bile duct obstruction, most patients present at a later stage with unresectable disease. The procedure involves resection of the distal pancreas containing the tumor with splenectomy and over-sewing of the distal pancreatic duct. Complications involve pancreatic stump leak, hemorrhage, and endocrine insufficiency. Laparoscopic exploration should precede attempted resection, because occult peritoneal metastases are common [16; 24].

Total Pancreatectomy

Total pancreatectomy, the least commonly performed procedure with the highest associated mortality (8.3%), may be needed to achieve an R0 resection margin for tumors in the neck of the pancreas, especially with extension into the body or tail, and in multifocal PDAC. Total pancreatectomy may be an option to pancreatic anastomosis in highly selected patients with a high-risk pancreas (small pancreatic duct) and obese patients with pancreatic fat infiltration. The metabolic consequences of permanent exocrine insufficiency and diabetes have a detrimental impact on quality of life and long-term survival [16; 24; 102].

Vascular Resection

Vascular involvement has traditionally been a formal contraindication to resection. With recent advances, venous resection and reconstruction can achieve R0 resection with similar overall survival and morbidity compared to surgery without venous resection. However, arterial resection during Whipple is associated with increased mortality and morbidity (bowel ischemia, hemorrhage, thrombosis) and is generally not recommended [16].

Progress in neoadjuvant therapies may downstage some tumors with arterial invasion to borderline resectable or resectable disease, making resection more achievable. Despite these advancements, it is currently accepted that arterial reconstruction is only appropriate in highly selected patients in high-volume centers with surgeons who are familiar with the advanced techniques required for reconstruction [16].

Total pancreatectomy should be considered in patients with locally advanced tumors who undergo pancreatectomy with arterial resection and reconstruction [16].

Biliary Drainage

In most patients with jaundice, early resection without biliary drainage is preferred. Preoperative drainage is indicated in patients with cholangitis or with obstructive jaundice scheduled for neoadjuvant therapy. Endoscopic retrograde placement of a fully covered metal stent is preferred. Endoscopic ultrasonography-guided stent placement is an effective and safe alternative [16].

CHEMOTHERAPIES IN PANCREATIC CANCER

As mentioned, the backbone of PDAC treatment is chemotherapy. Most patients present with advanced disease, and even those who undergo resection will require adjuvant chemotherapy. Chemotherapy is also used as neoadjuvant therapy and in metastatic disease with first-line or second-line indications [11].

Until recently, chemotherapies found effective in other GI cancers were applied to patients with advanced PDAC; the few agents showing any response became adjuvant therapies in localized PDAC. The near-futility in effective chemotherapy and redundancy in agents used in localized and metastatic PDAC reflects the pathologic complexity of this cancer and its profound resistance to cytotoxic therapies [2].

Since 2010, chemotherapy effectiveness has improved with the introduction of combination regimens, the identification of patients in whom mutational status conferred improved response to existing chemotherapies, and the introduction of novel compounds explicitly targeting mutational-related advanced PDAC.

FDA-Approved Chemotherapies in PDAC

Which chemotherapy agent/regimen has the strongest recommendation and level of evidence for use in patients with stage 3 (locally advanced) PDAC?

In addition to single chemotherapy agents, the FDA has approved regimens of these agents, including FOLFIRINOX (consisting of folinic acid [also referred to as leucovorin], fluorouracil [5-FU], irinotecan [IRN], and oxaliplatin [OX]) (***Table 9***) [3; 24; 80; 99]. Available chemotherapies are associated with acute and delayed toxicities, some of which can be dose-limiting (***Table 10***). ***Table 11*** summarizes the 2021 NCCN guideline for chemotherapy and chemoradiotherapy in PDAC.

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the American Society of Clinical Oncology, all patients with resected pancreatic adenocarcinoma who did not receive preoperative therapy should be offered six months of adjuvant chemotherapy in the absence of medical or surgical contraindications. The mFOLFIRINOX regimen is preferred in the absence of concerns for toxicity or tolerance.

(https://ascopubs.org/doi/10.1200/JCO.19.00946. Last accessed August 19, 2021.)

Strength of Recommendation/Level of Evidence: Strong/high

Fluoropyrimidines

Fluorouracil is a fluorinated (fluoro)-pyrimidine antimetabolite that inhibits thymidylate synthase and interferes with RNA synthesis and function, with some effect on DNA.

Capecitabine is an oral fluoropyrimidine that undergoes hepatic hydrolysis to form fluorouracil. The final enzyme, thymidine phosphorylase, is present at higher levels in tumor tissue, providing better selectivity and tolerability.

Gemcitabine is a pyrimidine antimetabolite that inhibits DNA polymerase and ribonucleotide reductase, which in turn inhibit DNA synthesis, blocks DNA replication and several forms of DNA repair [3; 24; 80; 99].

Erlotinib

Erlotinib is a human epidermal growth factor receptor type 1/epidermal growth factor receptor (HER1/EGFR) tyrosine kinase inhibitor. EGFR is expressed on the cell surface of normal cells and cancer cells. Erlotinib inhibits intracellular phosphorylation, which prevents further downstream signaling, resulting in cell death [3; 24; 80; 99].

Paclitaxel

Paclitaxel protein bound is a microtubular inhibitor (albumin-conjugated formulation) and a natural taxane that prevents depolymerization of cellular microtubules, which results in DNA, RNA, and protein synthesis inhibition [3; 24; 80; 99].

Irinotecan Liposomal

Irinotecan and its active metabolite SN-38 bind reversibly to the topoisomerase-1 DNA complex and prevent re-ligation of the single-strand breaks, leading to exposure time-dependent double-strand DNA damage and cell death. Irinotecan liposomal is used in combination with fluorouracil and leucovorin [3; 24; 80; 99].

CHEMOTHERAPY PROTOCOLS IN PANCREATIC CANCER			
Drug	**Dose and route**	**Administration**	**Given on days**
Gemcitabine Indication: Nonmetastatic PDAC Cycle length: 4 weeks (once weekly for 3 weeks, then 1 week off)			
Gemcitabine	1,000 mg/m^2 IV	Dilute in 250 mL NS (concentration ≤40 mg/mL), administered over 30 minutes.	Days 1, 8, and 15
Gemcitabine and capecitabine (GemCap) Indication: Adjuvant therapy Cycle length: 28 days Duration: 6 months			
Gemcitabine	1,000 mg/m^2 IV	Dilute in 250 mL NS (concentration ≤40 mg/mL), administered over 30 minutes.	Days 1, 8, and 15
Capecitabine[a]	830 mg/m^2 per dose oral	Twice daily (total 1,660 mg/m^2 per day), 12 hours apart. Swallow with water within 30 minutes post-meal.	Days 1 through 21
Modified FOLFIRINOX Cycle length: 14 days			
Oxaliplatin[b]	85 mg/m^2 IV	Dilute in 500 mL D5W, administer over 2 hours (before leucovorin). Shorter schedules (e.g., 1 mg/m^2 per minute) appear safe.	Day 1
Leucovorin	400 mg/m^2 IV	Dilute in 250 mL normal saline or D5W, administer over 2 hours (after oxaliplatin).	Day 1
Irinotecan[c]	150 mg/m^2 IV	Dilute in 500 mL normal saline or D5W, administer over 90 minutes concurrent with the last 90 mins of leucovorin infusion, in separate bags, using Y-line connection.	Day 1
Fluorouracil	2,400 mg/m^2 IV	Dilute in 500–1,000 mL 0.9% normal saline or D5W, administered as continuous IV infusion over 46 hours.[d]	Day 1
FOLFIRINOX Indication: Metastatic PDAC Cycle length: 14 days			
Oxaliplatin[b]	85 mg/m^2 IV	Dilute in 500 mL D5W, administer over 2 hours (before leucovorin). Shorter schedules (e.g., 1 mg/m^2 per minute) appear safe.	Day 1
Leucovorin	400 mg/m^2 IV	Dilute in 250 mL normal saline or D5W, administer over 2 hours (after oxaliplatin).	Day 1
Irinotecan[c]	150 mg/m^2 IV	Dilute in 500 mL normal saline or D5W, administer over 90 minutes concurrent with the last 90 mins of leucovorin infusion, in separate bags, using Y-line connection.	Day 1
Fluorouracil	400 mg/m^2 IV bolus	Give undiluted (50 mg/mL) as a slow IV push over 5 minutes (immediately after leucovorin).	Day 1
Fluorouracil	2400 mg/m^2 IV	Dilute in 500–1,000 mL 0.9% normal saline or D5W, administer as continuous IV infusion over 46 hours (immediately after IV bolus).[d]	Day 1

[a]Capecitabine is contraindicated in patients with known DPD deficiency.
[b]Many centers routinely infuse oxaliplatin via central venous line because of local pain with infusion into a peripheral vein
[c]Consider a lower dose of irinotecan with poor performance status.
[d]To accommodate an ambulatory pump for outpatients, can be administered undiluted (50 mg/mL) or the total dose diluted in 100–150 mL normal saline.

Source: [98; 105] *Table 9*

ACUTE AND DELAYED CHEMOTHERAPY TOXICITIES[a]		
Agent	**Acute Toxicities**	**Delayed Toxicities**
Fluorouracil	Nausea and vomiting Diarrhea	Oral and GI ulcers Bone marrow depression Diarrhea (especially with leucovorin) Neurologic defects, usually cerebellar Cardiac arrhythmias Palmar-plantar erythrodysesthesia (hand-foot syndrome)
Capecitabine	Nausea and vomiting	Hand-foot syndrome Diarrhea Stomatitis Dermatitis Bone marrow depression Hyperbilirubinemia
Gemcitabine	Fatigue Nausea and vomiting Fever	Bone marrow depression Edema Pulmonary toxicity
Irinotecan	Diarrhea	Diarrhea Leukopenia
Oxaliplatin	Peripheral sensory neuropathy Pharyngolaryngeal dysesthesias Paresthesias	Bone marrow depression Diarrhea Persistent neuropathy
Paclitaxel	Hypersensitivity reactions	Bone marrow depression Peripheral neuropathy Alopecia Arthralgias
[a]Dose-limiting toxicities are bold-faced.		
Source: [106; 107]		*Table 10*

DNA Damage Repair Mutational Status and Targeted Therapies

Platinum agents (e.g., cisplatin, oxaliplatin) and olaparib are recommended in patients with mutation in DNA damage repair (DDR) genes by the NCCN. DDR mutations are present in up to 24% of PDACs, most commonly *BRCA1/2* and *PALB2*. Germline *BRCA1/2* mutations (gBRCAm) affect approximately 7% of patients with PDAC [108]. DDR genes encode for proteins in the homologous repair pathway and DNA double-stranded break repair; thus, mutations may be more sensitive to further DNA damage [99].

Cisplatin inhibits DNA synthesis by the formation of DNA cross-links; denatures the double helix; covalently binds to DNA bases; and disrupts DNA function. Oxaliplatin is an alkylating agent. Following intracellular hydrolysis, the compound binds to DNA, forming cross-links that inhibit DNA replication and transcription, resulting in cell death [24; 99].

PDACs with DDR mutations demonstrate improved responses to platinum-based therapies, and patients with advanced PDAC showed significantly improved median overall survival (22 months vs. 9 months) compared with nonplatinum therapy [96].

Poly (ADP-ribose) polymerase (PARP) inhibition has been posited to act synergistically with *BRCA1/2* mutations by inhibiting single-stranded break repair, causing an accumulation of DNA damage and tumor-cell death [99; 109]. Olaparib is a PARP inhibitor FDA-approved for PDAC with gBRCAm as maintenance therapy to sustain a progression-free state during platinum-based chemotherapy in metastatic PDAC [96].

The NCCN expands the use of olaparib to PDAC with gPALB2m. There are calls to expand these agents to PDACs with somatic DDR mutations [108].

NCCN TREATMENT SUMMARY FOR PDAC		
Strength of Recommendation/ Evidence	**Regimen**	**Notes[a]**
Adjuvant stage 1 (resectable)		
Category 1	Gemcitabine Gemcitabine/capecitabine 5-FU/leucovorin	–
Category 2a	5-FU continuous infusion Chemoradiation	Chemoradiation should follow induction chemotherapy, with or without subsequent chemotherapy
Category 2B	Capecitabine	–
Neoadjuvant stage 1/2 (resectable or borderline resectable)		
Category 2A	Gemcitabine/paclitaxel NAB	–
Category 2B	Gemcitabine/cisplatin[b] FOLFIRINOX Chemoradiation	–
Stage 3 (locally advanced)		
Category 1	Gemcitabine	Preferred for patients with poor ECOG PS (≥ 2)
Category 2A	Gemcitabine/paclitaxel NAB Gemcitabine/erlotinib Gemcitabine/cisplatin[b] Gemcitabine/capecitabine Gemcitabine fixed-dose rate FOLFIRINOX Chemoradiation	Fixed-dose rate gemcitabine is a category 2B recommendation for patients with poor ECOG PS (≥ 2) Chemoradiation should follow induction chemotherapy, with or without subsequent chemotherapy
Category 2B	Gemcitabine/docetaxel/capecitabine Capecitabine 5-FU continuous infusion FOLFOX	–
Stage 4 (metastatic)		
Category 1	Gemcitabine Gemcitabine/paclitaxel NAB (preferred) Gemcitabine/erlotinib FOLFIRINOX (preferred)	–
Category 2A	Gemcitabine/cisplatin[b] Gemcitabine/capecitabine Gemcitabine fixed-dose rate Olaparib Pembrolizumab (for MSI-H or dMMR tumors only) Larotrectinib (for *NTRK*-positive only)	Fixed-dose rate gemcitabine is a category 2B recommendation for patients with poor ECOG PS (≥2) Olaparib for maintenance therapy only in *BRCA1/2* or *PALB2* mutated stage 4 disease without progression after 4 to 6 months of first-line platinum-based therapy
Category 2B	Gemcitabine/docetaxel/capecitabine Capecitabine[c] 5-FU continuous infusion[c] FOLFOX Entrectinib (for *NTRK*-positive only)	–

Table 11 continues to next page.

NCCN TREATMENT SUMMARY FOR PDAC *(Continued)*		
Strength of Recommendation/ Evidence	**Regimen**	**Notes[a]**
Second-line therapy		
Category 1	Gemcitabine[c,d] 5-FU/leucovorin/irinotecan[d]	–
Category 2A	Gemcitabine fixed-dose rate	Fixed-dose rate gemcitabine is a category 2B recommendation for patients with poor ECOG PS (≥ 2)
Category 2B	Capecitabine[c,e] 5-FU continuous infusion[c,e]	–
Strength of Recommendation Definitions		
Category	**Definition**	
1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.	
2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.	
2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.	
[a]ECOG performance status (PS) 0/1 only, unless noted. [b]In *BRCA1/2* or *PALB2* mutations only. [c]Poor ECOG PS (≥2) only. [d]If prior non-gemcitabine-based therapy. [e]If prior gemcitabine-based therapy.		
Source: [11]		*Table 11*

Other FDA-Approved Targeted Therapies

The approved indications for the following agents are biomarker-defined, rather than by tumor site (e.g., pancreatic).

Pembrolizumab

Pembrolizumab is indicated in patients with microsatellite-instability-high (MSI-H) or dMMR mutations. Immune checkpoint inhibitors (ICIs) have efficacy in solid tumors with a high tumor mutational burden, and MSI-H or dMMR mutation solid tumors are associated with high tumor mutational burden. The ICI pembrolizumab is an anti-programmed death receptor-1 antibody that releases inhibition of the immune response, improving antitumor immunity [11; 96].

Pembrolizumab is approved for any solid tumor with MSI-H or dMMR mutation that progresses during treatment without any satisfactory alternative treatment options [11; 96]. This agent represented the first FDA approval (in 2017) with a biomarker-defined indication (i.e., agnostic of cancer site) [107]. Although this mutation is present in only about 1% of PDAC tumors, up to 83% of patients with dMMR PDAC respond to pembrolizumab [110].

Larotrectinib and Entrectinib

Larotrectinib and Entrectinib are neurotrophin receptor kinase (NTRK) inhibitors approved (in 2018 and 2019) for advanced, morbid, or unresectable solid tumors with NTRK fusion mutations, found in less than 1% of PDCAs [96].

The mutation product, TRK fusion protein, activates mitogen activated protein kinase-extracellular regulated kinase and phosphoinositide3 kinase-serine threonine signaling pathways, implicated in the oncogenesis of pancreatic cancer [96]. The NCCN recommends larotrectinib and entrectinib as first-line and subsequent treatment options for patients with NTRK gene fusion-positive locally advanced or metastatic PDAC [11].

Chemotherapy Efficacy: Localized Disease

A variety of data on chemotherapy efficacy are available, allowing for comparison of available agents in specific patient populations (***Table 12***). However, the terminology used can be confusing. Disease-free survival and progression-free survival are synonymous terms, and choice of the term used in this section will reflect the reference material. This is also the case with median survival and median overall survival. Unless noted otherwise, all patient outcomes are reported as median figures.

ADJUVANT CHEMOTHERAPY TRIALS IN RESECTABLE PDAC		
Phase III trial (Year)	**Chemotherapy Comparison**	**Median Survival (months)**
ESPAC-1 (2004)	5-FU vs. observation	21 vs. 15.5
CONKO-001 (2013)	Gemcitabine vs. observation	22.8 vs. 20.2
ESPAC-3 (2012)	Gemcitabine vs. 5-FU/leucovorin	46 vs. 39
ESPAC-4 (2017)	Gemcitabine/ capecitabine vs. gemcitabine alone	28 vs. 25.5
PRODIGE 24 (2018)	Modified FOLFIRINOX vs. gemcitabine	54.4 vs. 35
APACT (2019)	Gemcitabine/ paclitaxel vs. gemcitabine alone	40.5 vs. 36.2
5-FU = 5-fluorouracil.		
Source: [2]		*Table 12*

The CONKO-001 trial established gemcitabine as standard adjuvant chemotherapy. In this study, 354 patients were randomized to receive gemcitabine or observation after resection and followed a median 136 months. Gemcitabine led to a 24% improvement in overall survival, a 10.3% absolute improvement in 5-year survival (20.7% vs. 10.4%), and a 4.5% improvement in 10-year survival (12.2% vs. 7.7%), compared to observation [111; 112].

The ESPAC-3 trial showed the importance of completing the full post-resection adjuvant chemotherapy course (six cycles) in extending median overall survival of these patients compared with those not completing chemotherapy (28.0 months vs. 14.6 months) [96].

A continuation, ESPAC-4, found adding another fluoropyrimidine-based agent (capecitabine) to gemcitabine was superior to gemcitabine alone in median survival (28.0 months vs. 25.5 months) and five-year survival (28.8% vs 16.3%). A synergistic effect between gemcitabine and capecitabine on the DNA thymidylate enzyme was suggested [96].

PRODIGE-24 randomized 493 patients (ECOG performance status ≤1) with resected PDAC to modified FOLFIRINOX or gemcitabine for 24 weeks. At median 33.6 month follow-up, the disease-free survival with modified FOLFIRINOX was 21.6 months, compared with 12.8 months with gemcitabine [113]. Grade 3/4 toxicities were more frequent with mFOLFIRINOX (75.9%) than gemcitabine (52.9%). Nonetheless, the median 54.4-month overall survival with resection followed by mFOLFIRINOX is the longest survival reported to date with phase III results [5; 114].

Tolerance of adjuvant therapy remains a limitation, and patients commonly receive less than 50% of the planned dose, reflecting exposure to significant chemotherapy-related toxicity in patients experiencing substantial post-resection morbidity [2].

Chemotherapy Efficacy: Advanced/Metastatic Disease

First-Line Chemotherapy in Metastatic PDAC

5-FU has been used in pancreatic cancer treatment since the 1950s. Patients with advanced PDAC typically show response rates greater than 20% and median survival of 2.5 to 6 months [24; 80].

In 1997, gemcitabine replaced 5-FU as first-line treatment in metastatic PDAC by improving one-year survival rates (18% vs. 2%) and median overall survival (5.65 months vs. 4.41 months) [32]. Subsequently, numerous attempts to improve gemcitabine efficacy in metastatic PDAC have involved adding another cytotoxic drug [2; 96]. Some show marginal but statistically significant improvements in median survival over gemcitabine alone (***Table 13***).

The NCIC CTG PA.3 trial found a nonmeaningful clinical improvement with gemcitabine/erlotinib over gemcitabine alone in median overall survival (6.24 months vs. 5.91 months). Despite FDA approval for locally advanced/metastatic PDAC, the clinical impact of this modest gain with increased toxicity can be questioned [32; 96].

PRODIGE 4/ACCORD 11 demonstrated that patients with advanced PDAC and ECOG performance status ≤1 had better outcomes with FOLFIRINOX than gemcitabine in median overall survival (11.1 months vs. 6.8 months) and progression-free survival (6.4 months vs. 3.3 months). Following these findings, FOLFIRINOX became standard first-line therapy for candidate patients [2].

FOLFIRINOX was associated with more toxicities, but the six-month degradation in quality of life was better in FOLFIRINOX than gemcitabine (31% vs. 66%). Improved cancer control with FOLFIRINOX may be due to the inclusion of irinotecan, which has activity against PDAC and synergistic activity when given prior to 5-FU [96].

Finally, the MPACT study demonstrated an improvement of 1.8 months in both median overall survival and median progression-free survival with gemcitabine plus nab-paclitaxel versus gemcitabine alone, leading to another first-line option for metastatic PDAC [96].

FIRST-LINE CHEMOTHERAPY TRIALS IN METASTATIC PDAC		
Phase III Trial (Year)	**Chemotherapy Comparison**	**Median Survival (Months)**
Cullinan (1985)	5-FU vs. 5-FU/doxorubicin vs. 5-FU/doxorubicin/mitomycin	5.5 vs. 5.5 vs. 4.5
Burris (1997)	5-FU vs. gemcitabine	4.4 vs. 5.6
Tempero (2003)	Gemcitabine vs. gemcitabine fixed dose rate	5 vs. 8
Heinemann (2006)	Gemcitabine ± cisplatin	6.0 vs. 7.5
NCIC-CTG PA.3 (2007)	Gemcitabine ± erlotinib	5.9 vs. 6.2
Cunningham (2009)	Gemcitabine ± capecitabine	6.2 vs. 7.1
CALGB 80303 (2010)	Gemcitabine ± bevacizumab	5.9 vs. 5.8
SWOG S0205 (2010)	Gemcitabine ± cetuximab	5.9 vs. 6.3
PRODIGE 4 (2011)	Gemcitabine vs. FOLFIRINOX	6.8 vs. 11.1
MPACT (2013)	Gemcitabine ± nab-paclitaxel	6.7 vs. 8.5
Source: [2]		*Table 13*

Second-Line Chemotherapy in Metastatic PDAC

Second-line therapy primarily consists of doublet therapy using the alternative pyrimidine backbone to what was used in the first-line setting. In 2016, the NAPOLI-1 trial demonstrated that after progression on a first-line gemcitabine-containing regimen for metastatic PDAC, 5-FU/leucovorin plus nanoliposomal irinotecan improved overall survival from 4.2 months (with 5-FU/leucovorin alone) to 6.1 months. As with nab-paclitaxel, improving the delivery of traditional chemotherapies may lead to more effective treatments for individuals with pancreatic cancer [32].

The POLO trial examined targeted maintenance therapy in a biomarker-selected population. In patients with metastatic PDAC harboring germline *BRCA1/2* mutations who had not progressed on first-line platinum-based chemotherapy, those randomized to olaparib had improved median progression-free survival (7.4 months compared with 3.8 months with placebo), but olaparib did not improve median overall survival [109]. The median duration of response to olaparib was 6 months, but was more than 24 months in a subset of patients (23%), which is exceptional in metastatic PDAC [108].

In second-line chemotherapy after progression on a first-line regimen, there is considerable heterogeneity in the survival of patients, and predicting which patients will benefit is not established. The decision to pursue second-line chemotherapy should be individualized and based on the patient's goals and preferences. Factors influencing the choice of second-line therapy include the regimen used for first-line therapy, performance status and comorbidity, and mutation status [106].

RADIATION THERAPY FOR PANCREATIC CANCER

In addition to resection and chemotherapy, treatment of patients with PDAC may include radiation therapy or chemoradiotherapy. Unlike chemotherapy, the role of radiation therapy in the treatment of PDAC is uncertain. Radiation therapy is not a stand-alone treatment in local PDAC but is sequenced with chemotherapy as chemoradiotherapy.

Earlier adjuvant radiation therapy trials demonstrated an overall survival and disease-free survival benefit, but subsequent European chemoradiation studies showed negative findings [12]. Technical advances suggest increasing promise with radiation therapy, but multi-institutional randomized trials in PDAC have lagged [12].

Stereotactic body radiation therapy has promising local control and quality of life, and is being evaluated for locally advanced and borderline resectable PDAC. However, adjuvant stereotactic body radiation therapy remains investigational with high toxicity risk and is only recommended as part of a clinical trial [12].

In the absence of phase 3 trials directly comparing neoadjuvant treatment approaches with or without radiation, adjuvant and neoadjuvant chemoradiation in PDAC awaits definitive evidence. Several such trials are in progress [2; 12]. In particular, RTOG 0848 is expected to definitively clarify the role of post-resection radiotherapy [115].

Nonetheless, the prospective cohort and retrospective evidence suggestive of decreased local recurrence and disease progression is sufficient for ASTRO, the NCCN and ASCO to recommend radiation therapy. Standard radiation prescriptions in the neoadjuvant setting consist of daily treatments over the course of five or six weeks to a total dose of 50 –54 gray (Gy) [2].

EVIDENCE-BASED PRACTICE RECOMMENDATION

Following surgical resection of pancreatic cancer, adjuvant conventionally fractionated radiotherapy with chemotherapy in select high-risk patients (i.e., positive lymph nodes and margins regardless of tumor location within the pancreas) is conditionally recommended by the American Society for Radiation Oncology.

(https://www.practicalradonc.org/cms/10.1016/j.prro.2019.06.016/attachment/0e8abbe7-fcc6-4c5d-8b46-e81e636ce080/mmc1.pdf. Last accessed August 19, 2021.)

Strength of Recommendation/Level of Evidence: Conditional/low

The type and duration of chemotherapy given with radiation therapy for pancreatic cancer depends on the clinical stage, setting (neoadjuvant or adjuvant), performance status, and comorbidities. Patients with favorable performance status (0 or 1) are typically offered FOLFIRINOX prior to radiation therapy. Patients who are elderly or have a poor performance status (≥2) are typically offered gemcitabine or gemcitabine/nab-paclitaxel prior to radiation therapy. The duration (two to six months or longer) depends on patient tolerance and tumor response (i.e., no evidence of progression on chemotherapy). Common dose-limiting toxicities are diarrhea, neuropathy, and hematologic [12].

NEOADJUVANT THERAPY

Preoperative, or neoadjuvant, therapy is a major paradigm shift in treatment for patients with localized PDAC that offers the potential to lengthen survival while sparing patients unnecessary treatment-related morbidity using available treatments [116]. The rationale for neoadjuvant therapy differs somewhat by disease stage and clinical features.

Neoadjuvant therapy is recommended in upfront resectable disease with high-risk features of dissemination. This includes tumors in pancreas body and tail or >3–4 cm, ascites, large regional lymph nodes, CA19-9 levels >1,000 U/mL, severe weight loss, and extreme pain. For these patients, staging laparoscopy is recommended to identify liver and peritoneal metastases missed by MDCT in assessing resectability, with endoscopic ultrasonography-guided biopsy [7; 11; 15]. The next step is systemic neoadjuvant therapy (i.e., chemotherapy), post-neoadjuvant therapy CA19-9, and MDCT with contrast to reassess resectability (with some limitations). If R0 resection is feasible and there is no evidence of metastatic disease, surgery should be attempted [7; 11; 15].

In general, neoadjuvant therapy for patients who are candidates for resection is controversial [116]. Some oncology groups do not recommend neoadjuvant therapy in upfront resectable disease (except with high-risk features) until better evidence is available, but this stance has become less tenable as additional evidence supporting efficacy becomes available [7; 13; 15].

Even in patients with anatomically localized disease based on imaging and after complete resection with R0 margins, the high rates of distant failure after surgery for resectable PDAC indicates most patients already have systemic disease at the time of diagnosis. Current imaging fails to accurately assess the true burden of disease, missing occult metastases and under-staging patients [116].

Given this reality, systemic therapy is crucial, but many patients do not receive adjuvant therapy after resection. The high complication rates and potentially prolonged recovery with resection results in 25% to 50% of patients not receiving postoperative therapy [116]. However, systemic neoadjuvant therapy allows patients to receive therapy when they have better performance status and before the potential development of postoperative complications [116].

Neoadjuvant therapy also tests the tumor biology. Patients with aggressive tumors that progress and/or metastasize during neoadjuvant therapy are spared a futile operation. Due to their performance status, patients who do poorly on systemic neoadjuvant therapy would likely do poorly with surgery, resulting in mortality or serious perioperative morbidity precluding adjuvant therapy. Neoadjuvant therapy allows patients with resectable tumors who are poor surgical candidates time to medically and/or physically optimize before surgery.

Neoadjuvant therapy is not without its drawbacks. Eligibility for neoadjuvant therapy requires a tissue diagnosis, but the dense PDAC tumor stroma impedes tissue confirmation in approximately 15% of patients [116]. Further, neoadjuvant therapy means delaying surgery, with the possibility for local progression during neoadjuvant therapy into unresectable PDAC [15]. However, local progression almost always occurs concomitantly with development of systemic disease [116]. Essentially, better evidence is needed. Until phase III results are available, the poor outcomes of conventional treatment sequencing argue for the need for neoadjuvant therapy.

Borderline resectable pancreatic cancer is a recognized indication for neoadjuvant therapy, as this approach may shrink and make tumors more amenable for surgical resection with fewer complications and increased chance of R0 resection. Neoadjuvant therapy may minimize early non-detectable microscopic metastases, decrease lymph node involvement, and improve overall survival and outcomes [96].

Upfront Resectable/Borderline Resectable Tumor and Neoadjuvant Therapy

What radiation dose is recommended for neoadjuvant chemoradiation?

The NCCN recommends neoadjuvant therapy for patients with resectable or borderline resectable tumors. Treatment at or coordinated through a high-volume center is preferred, when feasible, and participation in a clinical trial is encouraged. The preferred neoadjuvant options are FOLFIRINOX with or without subsequent chemoradiation, or gemcitabine plus albumin-bound paclitaxel with or without subsequent chemoradiation [11]. For patients with *BRCA/PALB2* mutations, the preferred regimen is gemcitabine plus cisplatin (two to six cycles) with or without subsequent chemoradiation [11].

ASTRO guidelines for neoadjuvant chemoradiation specify a radiation dose of 4,500–5,040 cGy in 180–200 cGy fractions [12]. They recommend delivery of radiation therapy following two to six months of chemotherapy.

Locally Advanced Pancreatic Cancer and Neoadjuvant Therapy

Locally advanced pancreatic cancer accounts for 30% of newly diagnosed cases. With local involvement of adjacent critical blood vessels and presence of occult micrometastatic disease, locally advanced pancreatic cancer is generally considered surgically unresectable and incurable, and the standard of care is similar to metastatic disease [2].

However, the increased use of preoperative multiagent chemotherapy followed by chemoradiation has significantly expanded the pool of patients with locally advanced pancreatic cancer eligible for resection with curative intent, significantly improving the resectability and overall survival of these patients [117].

In a single-institution phase II trial, 49 patients with locally advanced pancreatic cancer received eight cycles of FOLFIRINOX followed by 50.4 Gy of photon radiation with capecitabine and losartan. Of these patients, 39 were brought to the operating room, 34 (69%) had their cancer removed, and of these, 30 patients (88%) had an R0 resection. Among patients who underwent resection, median progression-free survival and overall survival were 21.3 and 33 months, respectively, versus the 11- to 12-month historical overall survival [118].

Neoadjuvant therapy is associated with a downstaging-to-resection rate of greater than 30% in selected patients with locally advanced pancreatic cancer, with survival comparable to or better than initially resectable disease. For patients with arterial involvement, arterial divestment shows a lower morbidity and mortality rate than arterial resection and reconstruction [117].

Post-Neoadjuvant Therapy Restaging Evaluation of Resectability

Following neoadjuvant therapy, a restaging evaluation with pancreatic protocol MDCT is required to image tumor shrinkage and rule out local progression for resectability. However, post-neoadjuvant therapy imaging is not a reliable indicator of resectability due to its inability to distinguish post-treatment fibrosis from residual viable tumor [117]. Post-neoadjuvant therapy CA19-9 levels are predictive of tumor regression and should be used to guide decisions about suitability for surgical exploration for resection. Diagnostic laparoscopy should be routinely used to minimize nontherapeutic surgery rates [117].

Adjuvant Chemotherapy in Patients with Resected PDAC After Neoadjuvant Therapy

After resection of pancreatic cancer following neoadjuvant FOLFIRINOX, the benefit of adjuvant chemotherapy on overall survival is unclear. Although randomized controlled trial confirmation is needed, a 2020 multicenter, retrospective study provided informative results [119]. Of 520 patients (median age: 61 years; 53.7% male) who received a median of six neoadjuvant cycles of FOLFIRINOX, 343 (66.0%) received adjuvant chemotherapy. Adjuvant chemotherapy was FOLFIRINOX for 68 patients (19.8%), gemcitabine-based chemotherapy for 201 (58.6%), capecitabine for 14 (4.1%), a combination or other agents for 45 (13.1%), and unknown for 15 patients (4.4%). The median overall survival was 38 months after diagnosis and 31 months after surgery. No survival difference was found for patients who received adjuvant chemotherapy compared with those who did not (29 months in both groups).

In multivariable analysis, the interaction of lymph node stage with adjuvant therapy was statistically significant. In patients with pathology-proven node-positive disease, adjuvant chemotherapy was associated with improved overall survival (26 months vs. 13 months). For those with node-negative disease, adjuvant chemotherapy was not associated with improved survival (38 months vs. 54 months). These results suggest that adjuvant chemotherapy after neoadjuvant therapy FOLFIRINOX and resection of pancreatic cancer was associated with improved survival only in patients with pathology-proven node-positive disease [119].

LOCALLY ADVANCED PANCREATIC CANCER

Neoadjuvant therapy increasingly shows the ability to downstage locally advanced pancreatic cancer into resectable tumor, but until such approaches are employed beyond specialized PDAC research centers, most of these patients will remain unresectable [2].

Chemotherapy selection for patients with locally advanced pancreatic cancer is largely based on extrapolation from studies in metastatic PDAC. However, the natural history of locally advanced pancreatic cancer is less predictable than metastatic disease [120]. In an important autopsy study, 28% of patients with locally advanced pancreatic cancer at initial diagnosis died with localized disease only, from complications of locally destructive tumor growth [120]. Also noted, not all isolated metastases at initial diagnosis are harbingers of widespread metastatic disease, nor the greatest threat to patient survival compared with the primary tumor or cachexia [17].

In patients with locally advanced pancreatic cancer, even with progression, treatment should not simply mirror that in metastatic disease. Rather, it should be based on the pattern of progression (locoregional vs. disseminated), prior chemotherapy and/or radiation, and sequence of therapy (as well as performance status and comorbidity). For example, if a patient with locally advanced pancreatic cancer and a history of only chemotherapy as prior treatment later develops locoregional progression, radiation may be the appropriate modality [8].

Fluoropyrimidines and gemcitabine are the most commonly used agents in adjuvant chemoradiotherapy trials of locally advanced pancreatic cancer. These studies suggest that as a radiosensitizer, capecitabine is a well-tolerated regimen with comparable or superior outcomes compared with low-dose gemcitabine [8].

There is a potential role for maintenance capecitabine or gemcitabine-based chemoradiotherapy in improving quality of life for patients with locally advanced pancreatic cancer and stable disease after 12 weeks of induction gemcitabine/capecitabine chemotherapy [8].

In contrast to conventionally fractionated chemoradiotherapy, there is growing interest in using induction chemotherapy for systemic control, followed by a short course of stereotactic body radiotherapy early during treatment with minimum disruption to systemic therapy. This could be particularly beneficial to patients with predominant local symptoms [8].

The ASCO guidelines for patients with locally advanced pancreatic cancer include several strong recommendations related to chemoradiotherapy or stereotactic body radiation therapy [2; 8]. Specifically, it states that chemoradiotherapy or stereotactic body radiation therapy may be offered upfront rather than chemotherapy [8]. This approach is recommended for patients with local progression but no metastases, performance status ≤2, and favorable comorbid profile. It should also be offered to patients with response to an initial six months of chemotherapy or with stable disease who develop chemotherapy toxicities that are intolerable or cause a decline in performance status [8]. If patients respond or their disease has at least stabilized after six months of induction chemotherapy, chemoradiotherapy or stereotactic body radiation therapy may be offered as an alternative to continuing chemotherapy alone [8].

For patients with unresectable or locally advanced pancreatic cancer, definitive conventionally fractionated or dose-escalated radiation therapy with chemotherapy is used. For patients without systemic progression after four to six months (or longer) of chemotherapy, ASTRO recommends definitive radiation therapy [12]. The preferred dose is 5,040–5,600 cGy in 175–220 cGy fractions.

Local Ablative Radiation

With surgical resection considered the only potentially curative option but most patients harboring unresectable PDAC tumor, nonoperative local treatment options that can provide a similar benefit are needed. Emerging radiation techniques that address organ motion have enabled curative radiation doses delivered in patients with inoperable disease [121].

In one 2021 report, patients with locally advanced pancreatic cancer were treated with hypofractionated ablative radiation therapy, using respiratory gating, soft tissue image guidance, and other methods to address organ motion and limit the dose to surrounding luminal organs [121]. At baseline, 119 patients with locally advanced pancreatic cancer and median CA19-9 level >167 U/mL received four months of induction chemotherapy, followed by ablative radiation therapy. The median overall survival from diagnosis and ablative radiation therapy were 26.8 and 18.4 months. The 12- and 24-month overall survival following therapy were 74% and 38%, and the 12- and 24-month cumulative incidence of locoregional failure were 17.6% and 32.8% [121]. Postinduction CA19-9 decline was associated with improved locoregional control and survival. Grade 3 upper GI bleeding occurred in 10 patients (8%), with no grade 4 to 5 events. This cohort study of patients with inoperable locally advanced pancreatic cancer found that ablative radiation therapy following multiagent induction therapy was associated with durable locoregional tumor control and favorable survival [121].

METASTATIC DISEASE

Systemic chemotherapy can benefit patients with metastatic PDAC by improving disease-related symptoms and survival compared with best supportive care alone, but patients should understand that chemotherapy is palliative and not curative [80].

First-line chemotherapy in metastatic PDAC is highly consistent in clinical practice guidelines from ASCO, NCCN and ESMO. Treatment selection is based on PDAC mutation status, serum total bilirubin level, ECOG performance status, comorbidity profile, patient preference and a support system for aggressive medical therapy, and access to chemotherapy port and infusion pump management services for FOLFIRINOX or mFOLFIRINOX.

The initial chemotherapy selection for germline or somatic *HRR* gene mutation is a platinum-based chemotherapy regimen. For those with performance status ≤1 and serum bilirubin less than 1.5 times upper limit of normal, FOLFIRINOX or mFOLFIRINOX is preferred. Gemcitabine plus cisplatin can be used and probably has similar benefit. For patients with performance status 2, comorbidity that precludes intensive therapy, or a serum bilirubin more than 1.5 times upper limit of normal despite stenting, FOLFOX is preferred over FOLFIRINOX.

After at least 16 weeks of initial platinum-based chemotherapy without disease progression, chemotherapy should be discontinued and maintenance therapy with olaparib initiated for those with germline *BRCA* or *PALB2* mutation. For advanced PDAC with somatic (i.e., non-germline) *BRCA* or *PALB2* mutation, the benefit of olaparib maintenance therapy is not known and is under investigation.

For patients with an unknown (pending) *HRR* status, waiting until the germline or somatic mutation status is known is not recommend, given the rapidity of progression in most patients with newly diagnosed metastatic PDAC. These patients should be treated like *HRR* mutation carriers until results of genetic testing are available [80].

Patients with performance status ≤1, serum bilirubin less than 1.5 times upper limit of normal, and favorable comorbidity, FOLFIRINOX is preferred, with gemcitabine plus nabpaclitaxel a potentially less toxic alternative. Patients with serum bilirubin more than 1.5 times upper limit of normal despite placement of a stent should receive FOLFOX rather than a gemcitabine-containing regimen, because gemcitabine is hepatically metabolized and associated with greater toxicity with hepatic impairment. For patients with performance status 2, favorable/adequate comorbidity, and serum bilirubin level less than 1.5 times upper limit of normal, gemcitabine monotherapy is suggested; gemcitabine/capecitabine is another option.

Highly selected patients with performance status 2 due to heavy tumor burden should be treated with gemcitabine plus nabpaclitaxel, owing to its higher response rate. Dose and schedule adjustments should be made to minimize toxicities. In patients with performance status ≥3 or poorly controlled comorbidity (regardless of histology or *BRCA/PALB2* mutation status), systemic chemotherapy should only be offered on an individualized, case-by-case basis; supportive care should be emphasized.

PALLIATION AND SYMPTOMATIC MANAGEMENT

At diagnosis, the median survival for patients with locally advanced, unresectable pancreatic cancer is 8 to 12 months; with metastatic disease, this decreases to 3 to 6 months. For patients with locally advanced and metastatic disease, systemic chemotherapy can improve survival. In the best outcomes to date, FOLFIRINOX demonstrated an 11.1-month median survival [122].

Patients receiving chemotherapy often report better overall quality of life, but extended survival with chemotherapy may not reduce symptom burden. Because the pancreas is located in the central abdomen at the root of the mesentery, most patients suffer from a significant symptom burden and frequently require medical attention and hospitalization for symptom management. Typical patients will require numerous interventions targeting pain, anorexia and weight loss, depression and anxiety, biliary obstruction, gastric outlet obstruction, ascites, and venous thromboembolism [122].

All patients with newly diagnosed PDAC should have a full assessment of symptom burden, psychological status, and social supports as early as possible. Regardless of cancer stage and patient prognosis, early introduction to expert palliative and supportive care improves the social, psychological, and physical well-being of patients; decreases the intensity of medical interventions at the end of life; and ultimately improves survival [2].

Palliative care is an interdisciplinary specialty that is focused on preventing and relieving suffering, and supporting the best possible quality of life for patients and their families facing serious illness, such as pancreatic cancer. Palliative care specialist clinicians provide in-depth pain and symptom management, communication regarding goals of care, and coordinated care across settings and over time. Palliative care aims to relieve suffering in all stages of disease and can be provided in tandem with curative or life-prolonging treatments [122].

When initiated early in the disease course, palliative care improves clinical, quality of care, and survival outcomes. Furthermore, multiple studies have shown that palliative care services improve patients' symptoms, allow patients to avoid hospitalization and to remain safely and adequately cared for at home, lead to better patient and family satisfaction, and significantly reduce prolonged grief and post-traumatic stress disorder among bereaved family members. Palliative care also lowers costs and reduces rates of unnecessary hospitalizations, diagnostic and treatment interventions, and nonbeneficial intensive care when patients are near the end of life [122].

VENOUS THROMBOEMBOLISM PROPHYLAXIS

Pancreatic cancer is one of the highest-risk malignancies for venous thromboembolism (VTE), which includes deep venous thrombosis (DVT), pulmonary embolism, and visceral portal or superior mesenteric vein thrombi. The incidence of VTE is four- to seven-fold higher in PDAC. The risk is highest in the first three months after diagnosis; chemotherapy further increases the risk. In PDAC, VTE is strongly associated with higher short- and long-term mortality and high risk of recurrent VTE [122].

All patients should be educated about warning signs and symptoms of VTE. Physical examination of the legs for asymmetric pitting edema, erythema, and warmth is crucial in each office visit, and the threshold to perform a CT angiogram with tachycardia or pleuritic chest pain present should be extremely low [122].

Routine anticoagulation for primary VTE prevention is not indicated in ambulatory outpatients with pancreatic cancer and no other VTE risk factors [122]. In a patient with PDAC and documented VTE (symptomatic or incidentally found), early initiation of anticoagulation is the standard approach, and lifelong therapy should be considered. The decision to continue anticoagulation should be balanced against bleeding risk, cost of therapy, quality of life, life expectancy, and patient preference. Low-molecular-weight heparin or oral rivaroxaban, apixaban, or edoxaban is preferred to vitamin K antagonist or unfractionated heparin for long-term anticoagulation [122].

PERI-PANCREATIC COMPLICATIONS

Bile Duct Obstruction

Endoscopic retrograde stenting is superior to surgical or percutaneous approaches to address bile duct obstruction because of a more favorable adverse event rate. Self-expandable metal stents are preferred over plastic stents in patients with a life expectancy of more than three months in terms of patency duration, less therapeutic failure and need for reintervention, lower cholangitis incidence, and better patient quality of life. Patency rates between covered and uncovered metal stents are not significantly different [16]. Endoscopic ultrasonography-guided biliary drainage is an alternative if endoscopic biliary stent placement is unsuccessful or technically not feasible.

Gastric Outlet Obstruction

In patients with gastric outlet obstruction, endoscopic duodenal stenting allows a quick resumption of oral intake, with a low complication rate and a short recovery period. However, the need for reintervention is higher after duodenal stenting compared with that of palliative surgery. Endoscopic ultrasonography-guided gastrojejunostomy is an effective and safe alternative to surgery [16].

Ascites

Ascites in patients with metastatic PDAC may be due to peritoneal metastases. In patients with locally advanced tumors, ascites may be caused by portal vein thrombus if the tumor compresses the portal vein locally [122].

Patients with malignant ascites from pancreatic cancer can experience abdominal discomfort, nausea, vomiting, and dyspnea from the pressure of the fluid against the anterior abdominal wall and diaphragm. For most patients, survival is short, and the focus is symptom control. Symptom relief from intermittent paracentesis tends to be short-lived, and the procedure must be repeated for symptom relief. If reaccumulation requires more than once-weekly paracentesis, placement of a long-term drainage catheter is an option; complication rates are higher with indwelling catheters. Diuretics such as spironolactone and furosemide decrease the absorption of water and sodium in the kidneys and may provide some symptomatic relief [122].

PAIN CONTROL INTERVENTIONS

Pancreatic cancer is one of the most painful malignancies [85]. All patients with locally advanced and metastatic pancreatic cancer should be offered aggressive treatment of pain [8]. Adequate control of pain may be unsatisfactory due to significant variation in local practice [123].

Pain is often the major presenting symptom of the disease and can be a significant feature of advanced pancreatic cancer. Patients describe a gnawing mid-epigastric pain, which radiates bilaterally under the ribs and into the mid-back, owing to the proximity of pancreatic tumors to the celiac plexus. All patients should have the level of pain and degree of pain relief from analgesics addressed at every visit [122].

The ASCO recommends that patients with metastatic pancreatic cancer should be offered aggressive treatment of the pain and symptoms of the cancer and/or the cancer-directed therapy.

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Strength of Recommendation/Level of Evidence: Strong/intermediate

Pharmacotherapy

The mainstay of pain management is opioid therapy, and palliation of pain can often be successfully achieved by opioid analgesics alone [122]. Patients with moderate-to-severe pain should receive doses adequate to provide relief. Concern about addiction should not be a barrier to effective pain control; even with dose escalation, addiction is seldom a problem in patients with PDAC and the risk is lower than generally assumed in non-malignant pain [81; 123]. Given the ongoing concerns regarding opioid misuse in the United States, drug diversion may be a consideration. Accordingly, patients should be advised on safe storage strategies and disposal of any discontinued opioid or other controlled substance prescriptions to minimize diversion.

For patients with persistent nausea and vomiting for whom taking oral medications is difficult, pain control may be achieved using transdermal patches when adipose tissue is sufficient for transdermal absorption [122]. When pain is constant rather than intermittent, long-acting oral (e.g., morphine, oxycodone, oxymorphone) or transdermal (e.g., fentanyl, buprenorphine) preparations may work better [81]. Breakthrough pain can be treated with rapid-onset transmucosal or intranasal fentanyl formulations. Methadone may be advantageous in many patients and can be used in small doses as add-on to existing opioid treatment. Methadone should only by prescribed by clinicians who are familiar with the complex pharmacology and adverse effect profile of this opioid [123].

Laxatives should be considered for all patients on opioid analgesia for PDAC pain, because constipation is a nearly universal side effect. There is considerable individual variation in both efficacy and side effects. Not all patients benefit from or tolerate opioids. A trial of an alternative opioid may also be indicated. Cases of poor pain control or intolerable pain may benefit from continuous opioid infusion via epidural or intrathecal catheters [81; 123]. Adjunctive treatments, such as cannabinoids, ketamine, clonidine, benzodiazepines, anti-psychotics, gabapentin, pregabalin, nortriptyline, or duloxetine, warrant consideration [122].

Near the end of life, pain management for advanced and terminal PDAC can become very challenging, and an interdisciplinary approach including palliative care specialists is needed. It is important wherever possible to consider the preferences of the patient. A range of supportive care measures can be offered, including intensive home support, home care with parenteral opioids, patient-controlled analgesia, and palliative sedation [123].

Celiac plexus neurolysis offers medium-term relief, but other procedures (e.g., splanchnicectomy) are also available. Adjunctive treatments for pain, depression, and anxiety as well as radiotherapy, endoscopic therapy, and neuromodulation may be required. Palliative chemotherapy may provide pain relief as a collateral benefit [123].

Celiac Plexus Neurolysis

Neurolytic procedures reduce pain by destruction of the afferent pathways from the pancreas to the brain. One of the most commonly used procedures is celiac plexus neurolysis.

The celiac plexus is a dense network of nerves that innervates the upper abdominal organs. Pain may be relieved by inhibiting synaptic pathways within the plexus by chemical destruction of the pathways and ganglia using dehydrated alcohol. Celiac plexus neurolysis is performed under endoscopic ultrasonography guidance [122].

Celiac plexus neurolysis improves analgesia and quality of life and decreases opioid requirements. The analgesic effect seems to vanish after eight weeks, and in most patients, pain recurs after three months. Repeated celiac plexus neurolysis benefits about 30% of patients and is normally not offered [123].

Splanchnic Nerve Neurolysis

Splanchnicectomy may disrupt more nerve pathways than celiac plexus neurolysis and is a better option when there is a large mass in the region of the celiac plexus. Splanchnicectomy is seldom performed in patients with PDAC despite some evidence of long-lasting pain relief and few complications in observational series, possibly because the expertise is not widely available [123].

Radiation Therapy

External beam radiation therapy with or without concomitant chemotherapy may also significantly alleviate pain due to local invasion of pancreatic cancer, frequently with improvement in cachexia and obstructive symptoms. However, it may take several weeks to achieve its maximal effect. When pain is caused by liver or bone metastases, patients may benefit from radiation therapy [16; 122].

CACHEXIA, WEIGHT LOSS, AND NUTRITIONAL COMPROMISE

Nutritional compromise in PDAC is common, but the underlying pathologies are diverse [2]. Nausea, caused both by the primary disease process and its associated chemotherapy, is most effectively treated with serotonin-3 receptor antagonists and atypical antipsychotics (e.g., olanzapine), with some emerging evidence suggesting efficacy with cannabinoids. Loss of appetite, even in the absence of overt nausea, is frequently reported by patients, and this symptom is driven by central pathways that are largely distinct from those that produce nausea.

Malabsorption secondary to pancreatic exocrine deficiency degrades nutritional status. Pancreatic enzyme-replacement therapy helps to stabilize weight loss and also improves quality of life by decreasing gastrointestinal symptoms. Malabsorption from biliary obstruction is a complication found in up to 90% of patients with PDAC. Similar to the replacement of pancreatic enzymes, the treatment of biliary obstruction improves symptoms beyond its effects on digestion, including anorexia, pruritus, and fatigue.

Collectively, careful attention to the nutritional status of patients with PDAC improves both their survival and quality of life. Early and regular involvement of nutrition experts in their care is recommended [2; 124].

Cancer-Related Anorexia/Cachexia Syndrome (CACS)

A constellation of disproportionate loss of lean body mass, weight loss, muscle wasting, adipose tissue reprogramming, and anorexia, cancer-related anorexia/cachexia syndrome (CACS) is more frequent in patients with PDAC than in any other malignancy due to the complex metabolic profile of pancreatic cancer [2]. In a study of 390 patients with advanced cancers, the rate of cachexia was highest in PDAC (89%), followed by gastric cancer (76%) and esophageal cancer (53%) [125].

Unlike simple starvation, which is characterized by a caloric deficiency that can be reversed with appropriate feeding, the weight loss of cachexia cannot be adequately treated with aggressive feeding [126]. The physical impact of CACS contributes to decreased patient quality of life, treatment response, and survival due to gross alterations in protein metabolism, increased oxidative stress, and systemic inflammation. The psychological impact also contributes to decreased quality of life for both patients and their families [125].

In CACS, an abnormally accelerated resting energy expenditure increases muscle protein breakdown and lipolysis, which seems related to activation of cytokines (e.g., tumor necrosis factor-alpha, interleukin 6 and 1 beta), and tumor-derived, potentially cachexia-inducing factors that target skeletal muscle gene products [122; 126].

Potentially Beneficial Agents

Which agents have proven efficacy in the treatment of anorexia associated with cancer-related anorexia/cachexia syndrome?

Cachexia in itself does not respond to nutritional support. There are no FDA-approved medications for treatment of CACS, and positive pharmacotherapy response in patients with anorexia associated with non-malignant disease has been difficult to translate into benefit for patients with cancer [127; 128].

Many agents have been evaluated for the treatment of CACS, but only corticosteroids (e.g., dexamethasone) and progesterone analogs (e.g., megestrol acetate) have a proven benefit in the anorexia associated with this syndrome [122]. Selection is based on life expectancy and assessment of risks versus benefits. Dexamethasone is suggested for patients for whom only weeks of therapy are anticipated, while megestrol acetate or medroxyprogesterone acetate (another progesterone analog) are suggested for patients with longer life expectancies [126].

A phase III study randomized 190 patients with advanced cancer and anorexia to megestrol acetate (480 mg/day), dexamethasone (4 mg/day), or placebo for up to four weeks. Differences in primary endpoint (at least 25% improvement in appetite) between megestrol (79.3%), dexamethasone (65.5%), and placebo (58.5%) were non-significant. Hyperglycemia and deep vein thromboses were more frequent with dexamethasone than megestrol or placebo. No other differences from placebo were found [127].

In this trial, the higher rate of deep vein thromboses with dexamethasone was unexpected. Megestrol acetate is associated with thromboembolic events and is contraindicated in patients with VTE. Dexamethasone has the potential to reduce cancer-related fatigue and elevate mood, at the significant cost of accelerating catabolic effects on muscle [127]. The primary benefits associated with these drugs are increased appetite and weight gain, not improved survival, and both drugs are associated with potential harms [122].

Mirtazapine is well-known for promoting weight gain. A placebo-controlled randomized trial found that appetite scores increased similarly with mirtazapine (15 mg at night) and placebo during the 28-day study. Mirtazapine was associated with significantly less increase in depressive symptoms and higher prevalence of somnolence than placebo, but no other differences were found [128].

The evidence of benefit in patients with CACS is inconclusive for androgens and selective androgen receptor modulators, anamorelin, cyproheptadine, long-chain omega-3 fatty acids, vitamins, minerals, and other dietary supplements, nonsteroidal anti-inflammatory drugs (NSAIDs), thalidomide, and combination approaches [126]. However, a trial of low-dose olanzapine (5 mg/day) is reasonable, particularly for patients who have concurrent nausea and/or vomiting unrelated to chemotherapy or radiation therapy [126].

Cannabis and Cannabinoids

In the cannabis plant, delta9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the best-characterized therapeutic constituents. Pharmaceutical cannabinoid products containing THC (dronabinol), a THC analog (nabilone), or THC:CBD in an oromucosal spray (nabiximols, investigational) were examined for efficacy in CACS and palliative care in two meta-analyses [126].

Unfortunately, no benefit beyond placebo was found for pharmaceutical cannabinoid products in CACS, despite their superior weight gain and appetite effects in patients with advanced HIV [129]. Cancer patients with more than 30% decrease in pain with cannabinoids compared with placebo approached significance [129].

In both meta-analyses, available studies of smoked cannabis in CACS did not meet evidence thresholds and were excluded. This limits the ability to inform real-world clinical practice, where patient preference, self-titration to tolerability/effect, access, and other factors favor smoked/vaped cannabis over single-molecule pharmaceutical cannabinoids [130].

Counseling and Support

The substantial loss of body mass can cause significant distress to patients. Although advanced cachexia is irreversible, palliating anorexia in patients with advanced cancer is best approached by focusing on stimulating appetite, supporting each person's food preferences, and avoiding prescriptive dietary advice [127].

Providing education to patients and their caregivers is crucial. The objective is to promote a shared understanding about changed goals of care, and to help reduce the distress caused by reduced oral intake [127].

Family members in particular can require educational intervention, as their distress may manifest in attempts to pressure or coerce the patient into increased feeding. Key points to discuss with patients and their family members, related to interactions about nutrition and eating near the end of life, include the following [131]:

- Loss of appetite is common in patients with advanced cancer and may be the result of the cancer process itself.
- Trying to force a patient to eat is usually counterproductive, potentially leading to increased nausea/vomiting.
- In most patients with advanced cancer and cachexia, providing additional calories by feeding tubes and/or intravenously does not improve outcomes.
- Trying to make a patient eat, when they have marked appetite loss, can lead to decreased social interactions and increased patient distress regarding interactions with caregivers (including stories of patients, in their dying days, pretending to be asleep when relatives visit, so that the relatives do not try to make them eat something).

Caregivers should be advised that it may be best to listen to and support the patient in a variety of other ways (such as giving the patient a massage or applying a lip moisturizer) instead of trying to talk them into eating more. Referral to a registered dietitian may provide patients and caregivers with additional opportunities to discuss concerns and challenges related to nutrition, appetite, and meal planning.

Diabetes Mellitus in PDAC

The presence of diabetes has been associated with higher mortality in patients with PDAC; corticosteroids can induce or exacerbate diabetes in these patients. For patients with PDAC-related diabetes, nutritional management by an experienced dietitian is essential [16]. Metformin or insulin is used as a first-line therapy. Insulin is often the preferred agent because of its efficacy, flexibility, and safety.

Careful monitoring of plasma glucose levels two hours after meals is widely recommended. The limited literature on this topic recommends maintaining blood glucose levels to avoid hypoglycemia and reduce symptoms of hyperglycemia.

Pancreatic Exocrine Insufficiency and Pancreatic Enzyme Replacement Therapy (PERT)

A contributory factor to extreme weight loss may be pancreatic exocrine insufficiency, which leads to maldigestion, fat malabsorption, and steatorrhea. The main clinical manifestation is weight loss and malnutrition, and nonspecific symptoms such as abdominal cramping, flatulence, and urgency to defecate. Fat malabsorption does not become evident until pancreatic lipase secretion falls below 10% of normal levels [122].

Pancreatic exocrine insufficiency results from loss of pancreatic parenchyma and/or tumor obstruction of the main pancreatic duct, and can occur after surgery or irradiation. The characteristic fatty stools associated with steatorrhea (loose, greasy, foul-smelling) may not be evident because patients tend to limit fat ingestion [122].

Pancreatic exocrine insufficiency is very frequent (>90% with tumors in the pancreatic head), and is associated with higher mortality in patients with unresectable PDAC. Pancreatic enzyme replacement therapy (PERT) improves survival in these patients [16]. Given its high incidence, diagnostic testing is not necessary. Patients suspected of fat malabsorption should be treated empirically with oral PERT [122].

The classical approach to patients with pancreatic exocrine insufficiency was restricting fat intake (<20 gm/day) in an attempt to reduce steatorrhea. However, this further restricts the intake of fat-soluble vitamins, which are already malabsorbed in patients with pancreatic exocrine insufficiency, and is not recommended. Frequent low-volume meals and avoidance of foods that are difficult to digest (e.g., legumes) are generally recommended [122].

Pancreatic exocrine insufficiency is treated with capsules of porcine pancreatic enzymes (pancrelipase). There are a number of commercial products available, and the amount of enzyme per capsule varies [81]. Doses are in United States Pharmacopeia (USP) units or International Units (IU); 90,000 USP is equivalent to 30,000 IU [122]. A healthy pancreas produces about 900,000 USP of lipase in response to a meal. Sufficient fat absorption can be maintained at around 10% of normal capacity; thus, roughly 90,000 USP per meal is needed. Because non-resected patients retain some pancreatic function, a starting dose of 75,000 USP with main meals and 25,000 with snacks should suffice in reducing steatorrhea and preventing weight loss. Enzymes are most effective when taken across the course of a meal. Following Whipple, patients will require 90,000 USP with meals and 45,000 USP with snacks [124].

Acidic gastric pH is normally neutralized by pancreatic bicarbonate secretion, which is absent in many patients with PDAC, especially following Whipple resection. Acid-suppressing therapy with a proton pump inhibitor is often required, as failure to neutralize gastric acid inactivates the enzymes [16; 124].

Despite recommendation from expert groups, including the NCCN, evidence suggests PERT is underutilized. This was examined in a large commercially insured U.S. population from 2001–2013. Among patients with PDAC (32,461), 1.9% had diagnostic testing for exocrine insufficiency, 21.9% filled a prescription for PERT, and 5.5% were prescribed an adequate dose (defined as ≥120,000 USP lipase daily) [132].

Testing and appropriate dosing is infrequent and inconsistent in an insured U.S. population. Efforts are needed to educate medical providers on the best practices for managing exocrine pancreatic insufficiency in these patients [132].

CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

For patients who are not proficient in English, it is important that information regarding all aspects of their care (including diagnostic procedures and treatment options) and palliative care resources be provided in their native language, if possible. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required. Interpreters can be a valuable resource to help bridge the communication and cultural gap between patients and practitioners. Interpreters are more than passive agents who translate and transmit information back and forth from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers who ultimately enhance the clinical encounter. In any case in which information regarding treatment options and medication/treatment measures are being provided, the use of an interpreter should be considered. Print materials are also available in many languages, and these should be offered whenever necessary.

CONCLUSION

PDAC is the most lethal solid malignancy, predicted to become the second leading cause of cancer death in the United States by 2030. The complexity of this aggressive cancer has been vexing to investigators and tragic for patients and their families. Major research efforts over the past 50 years have only marginally improved the five-year survival rate from 6% to 10.8%. The greatest gains—from resection of early-stage tumors—are the least likely to present at diagnosis. There is an urgent need to reduce PDAC incidence through primary and secondary prevention, and mortality by accelerating therapeutic development [133].

Until diagnostic or therapeutics breakthroughs arrive, novel uses of standard treatments (i.e., neoadjuvant therapy) show survival advantages for a greater number of patients. The longest survival reported by a phase III trial was published in 2018—a median 54.4 months in patients who received resection followed by mFOLFIRINOX [113]. Many novel treatments are in phase III trials. Additional approaches to manage morbidities and provide better palliative care are also needed. Cancer anorexia/cachexia is a high-priority area.

It is now clear that even early-stage PDAC is a systemic disease and that new-onset metabolic (e.g., diabetes, anorexia/cachexia, hyperglycemia) and neuropsychiatric (e.g., depression, fatigue) symptoms/syndromes are prodromal rather than comorbid or secondary. This recognition has also called for a re-thinking of pancreatic cancer from a more integrative, multi-system perspective [2].

Customer Information/Evaluation insert located between pages 32–33.

Course Availability List

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POSTOPERATIVE COMPLICATIONS

UPDATE

#30763 • 15 ANCC / 1 Pharm Hour

Book By Mail – $98 • ONLINE – $90

Purpose: The purpose of this course is to provide nurses and all allied health professionals who care for postsurgical patients the knowledge necessary to recognize and manage common postoperative complications, improving patient care and outcomes.
Faculty: Susan Engman Lazear, RN, MN
Audience: This course is designed for all nurses and allied professionals involved in the care of patients who undergo surgical procedures, especially those who work in the preoperative area, the operating room, or the postanesthesia unit in hospitals or free-standing surgical centers.
Additional Approval: AACN Synergy CERP Category A, CCMC

ACUTE CORONARY SYNDROME: AN OVERVIEW FOR NURSES

#30993 • 15 ANCC / 10 Pharm Hours

Book By Mail – $98 • ONLINE – $90

Purpose: The purpose of this course is to reduce the widening gap between care according to guidelines and actual care delivered by providing nurses with knowledge necessary to implement the most appropriate approach to diagnosis and treatment.
Faculty: Karen Majorowicz, RN; Lori L. Alexander, MTPW, ELS, MWC
Audience: This course is designed for nurses practicing in primary care, inpatient, outpatient, and home care settings to enhance their knowledge of the evidence-based guidelines related to the assessment, management, and secondary prevention of acute coronary syndrome.
Additional Approval: AACN Synergy CERP Category A, CCMC

PRESSURE INJURIES AND SKIN CARE

UPDATE

#34344 • 5 ANCC Hours

Book By Mail – $38 • ONLINE – $30

Purpose: The purpose of this course is to provide nurses with the information necessary to accurately identify, treat, and manage skin breakdown (pressure ulcers), thereby improving patient outcomes and quality of life.
Faculty: Maryam Mamou, BSN, RN, CRRN, CWOCN
Audience: This course is designed for nurses in all practice settings, particularly those caring for patients at high risk for developing pressure injuries.
Additional Approval: AACN Synergy CERP Category A, CCMC

COLORECTAL CANCER

UPDATE

#90782 • 15 ANCC / 5 Pharm Hours

Book By Mail – $98 • ONLINE – $90

Purpose: The purpose of this course is to provide healthcare professionals with information regarding the screening, diagnosis, and treatment of colorectal cancer in order to improve adherence to established guidelines and, by extension, patient outcomes.
Faculty: Mark Rose, BS, MA, LP
Audience: This course is designed for physicians, physician assistants, nurses, and other healthcare providers who may improve the identification and care of patients with colorectal cancer.
Additional Approval: AACN Synergy CERP Category A, CCMC

HIPAA PRIVACY AND SECURITY

NEW!

#91140 • 5 ANCC Hours

Book By Mail – $38 • ONLINE – $30

Purpose: The purpose of this course is to provide information that will allow health and mental health professionals to more easily comply with the Privacy and Security Rules defined by HIPAA.
Faculty: Carol Shenold, RN, ICP
Audience: This course is designed for all members of the interprofessional healthcare team.
Additional Approval: AACN Synergy CERP Category B

SMOKING AND SECONDHAND SMOKE

UPDATE

#91784 • 10 ANCC / 5 Pharm Hours

Book By Mail – $68 • ONLINE – $60

Purpose: The purpose of this course is to provide physicians, nurses, behavioral health professionals, and other members of the interdisciplinary team with a formal educational opportunity that will address the impact of tobacco smoking and secondhand exposure in public health and disease as well as interventions to promote smoking cessation among their patients.
Faculty: Mark S. Gold, MD, DFASAM, DLFAPA
Audience: This course is designed for physicians, nurses, and other healthcare professionals who may intervene to stop patients from smoking.
Additional Approval: AACN Synergy CERP Category A, CCMC

Prices are subject to change. Visit www.NetCE.com for a list of current prices.

Course Availability List *(Cont'd)*

OSTEOARTHRITIS

#94954 • 10 ANCC / 5 Pharm Hours

Book By Mail – $68 • ONLINE – $60

Purpose: The high prevalence of osteoarthritis and its substantial burden at both the individual and healthcare system levels demands sound knowledge and clinical skills in diagnosing and managing the disease. The purpose of this course is to provide healthcare professionals with the information necessary to adequately assess osteoarthritis symptoms, treat osteoarthritis patients based on evidence-based guidelines, and appropriately refer to specialists.
Faculty: Lori L. Alexander, MTPW, ELS, MWC
Audience: This course is designed for physicians, physician assistants, nurses, and other healthcare professionals involved in the care of patients with osteoarthritis.
Additional Approval: AACN Synergy CERP Category A, CCMC

SUBSTANCE USE DISORDERS AND PAIN MANAGEMENT: MATE ACT TRAINING

#95300 • 8 ANCC / 8 Pharm Hours

Book By Mail – $56 • ONLINE – $48

Purpose: The purpose of this course is to provide clinicians who prescribe or distribute controlled substances with an appreciation for the complexities of managing patients with substance use disorders and comorbid pain in order to provide the best possible patient care and to prevent a growing social problem.
Faculty: Mark Rose, BS, MA, LP
Audience: This course is designed for all healthcare professionals who may alter prescribing practices or intervene to help meet the needs of patients with substance use disorders.
Additional Approval: AACN Synergy CERP Category A
Special Approval: This course is designed to meet the Federal MATE Act requirement for new or renewing DEA licensees to complete 8 hours of training on opioid or other substance use, disorders, and the appropriate treatment of pain.

OPIOID SAFETY: BALANCING BENEFITS AND RISKS

#95500 • 5 ANCC / 5 Pharm Hours

Book By Mail – $38 • ONLINE – $30

Purpose: The purpose of this course is to provide clinicians who prescribe or distribute opioids with an appreciation for the complexities of opioid prescribing and the dual risks of litigation due to inadequate pain control and drug diversion or misuse in order to provide the best possible patient care and to prevent a growing social problem.
Faculty: Mark Rose, BS, MA, LP
Audience: This course is designed for all physicians, osteopaths, physician assistants, pharmacy professionals, and nurses who may alter prescribing and/or dispensing practices to ensure safe opioid use.
Additional Approval: AACN Synergy CERP Category A
Special Approval: This course fulfills the 2-hour requirement for pain management, identification of addiction, or the practices of prescribing or dispensing opioids for Pennsylvania CRNPs with prescriptive authority.

SUICIDE ASSESSMENT AND PREVENTION

#96442 • 6 ANCC Hours

Book By Mail – $44 • ONLINE – $36

Purpose: The purpose of this course is to provide health and mental health professionals with an appreciation of the impact of depression and suicide on patient health as well as the skills necessary to identify and intervene for patients at risk for suicide.
Faculty: Mark Rose, BS, MA, LP
Audience: This course is designed for physicians, nurses, pharmacists, and other healthcare professionals who may identify persons at risk for suicide and intervene to prevent or manage suicidality.
Additional Approval: AACN Synergy CERP Category A, CCMC

PSYCHEDELIC MEDICINE AND INTERVENTIONAL PSYCHIATRY

#96790 • 10 ANCC / 8 Pharm Hours

Book By Mail – $68 • ONLINE – $60

Purpose: The purpose of this course is to provide medical and mental health professionals with the knowledge and skills necessary to effectively treat mental disorders using emerging psychedelic and interventional techniques.
Faculty: Mark S. Gold, MD, DFASAM, DLFAPA
Audience: The course is designed for all members of the interprofessional team, including physicians, physician assistants, nurses, and mental health professionals, involved in caring for patients with mental disorders resistant to traditional treatment approaches.
Additional Approval: AACN Synergy CERP Category A

CANNABIS AND CANNABIS USE DISORDERS

#96973 • 5 ANCC / 5 Pharm Hours

Book By Mail – $38 • ONLINE – $30

Purpose: The purpose of this course is to allow healthcare professionals to effectively identify, diagnose, treat, and provide appropriate referrals for patients with cannabis use disorders.
Faculty: Mark Rose, BS, MA, LP
Audience: This course is designed for health and mental health professionals who are involved in the evaluation or treatment of persons who use cannabis, either illicitly or as an adjunct to medical treatment.
Additional Approval: AACN Synergy CERP Category A

Prices are subject to change. Visit www.NetCE.com for a list of current prices.

Course Availability List *(Cont'd)*

IMPLICIT BIAS IN HEALTH CARE

NEW!

#97000 • 3 ANCC Hours

Book By Mail – $26 • ONLINE – $18

Purpose: The purpose of this course is to provide healthcare professionals an overview of the impact of implicit biases on clinical interactions and decision making.
Faculty: Alice Yick Flanagan, PhD, MSW
Audience: This course is designed for the interprofessional healthcare team and professions working in all practice settings.
Additional Approval: AACN Synergy CERP Category B

COMMONLY ABUSED SUPPLEMENTS

NEW!

#98020 • 2 ANCC Hours

Book By Mail – $23 • ONLINE – $15

Purpose: The purpose of this course is to provide healthcare professionals in all practice settings the knowledge necessary to increase their understanding of the commonly abused supplements and their adverse effects.
Faculty: Chelsey McIntyre, PharmD
Audience: This course is designed for healthcare professionals whose patients are taking or are interested in taking dietary supplements.
Additional Approval: AACN Synergy CERP Category A

GETTING TO THE POINT: ACUPUNCTURE AND ACUPOINT THERAPIES

NEW!

#98030 • 4 ANCC Hours

Book By Mail – $32 • ONLINE – $24

Purpose: The purpose of this course is to provide healthcare professionals in all practice settings the knowledge necessary to increase their understanding of acupoint and acupressure therapies.
Faculty: Chelsey McIntyre, PharmD
Audience: This course is designed for healthcare professionals whose patients are using or are interested in using acupoint and acupressure therapies.
Additional Approval: AACN Synergy CERP Category A

DIZZINESS AND VERTIGO

#98401 • 10 ANCC / 5 Pharm Hours

Book By Mail – $68 • ONLINE – $60

Purpose: The purpose of this course is to provide clinicians with the information necessary to appropriately diagnose and treat causes of dizziness and vertigo and improve patients' quality of life.
Faculty: Mark Rose, BS, MA, LP
Audience: This course is designed for physicians and nurses involved in the diagnosis, treatment, and care of patients with dizziness and/or vertigo.
Additional Approval: AACN Synergy CERP Category A, CCMC

PARKINSON DISEASE

UPDATE

#98772 • 10 ANCC / 5 Pharm Hours

Book By Mail – $68 • ONLINE – $60

Purpose: The purpose of this course is to provide physicians, nurses, and other members of the interprofessional healthcare team a review of pathogenesis, disease progression, diagnosis, and management of Parkinson disease, in order to improve patient care and quality of life.
Faculty: Mark Rose, BS, MA, LP
Audience: This course is designed for all healthcare providers in the primary care setting who may encounter patients with Parkinson disease.
Additional Approval: AACN Synergy CERP Category A, CCMC

ANEMIA IN THE ELDERLY

#99083 • 5 ANCC / 2 Pharm Hours

Book By Mail – $38 • ONLINE – $30

Purpose: The purpose of this course is to provide healthcare providers with the knowledge and tools necessary to identify anemia early and respond appropriately. Better health outcomes for the geriatric population will result from an increase in evidence-based clinical practices.
Faculty: Susan Waterbury, MSN, FNP-BC, ACHPN
Audience: This course is designed for physicians, physician assistants, nurses, and other healthcare professionals involved in the care of elderly patients.
Additional Approval: AACN Synergy CERP Category A, CCMC

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☐	35270	Multimodal Pharmacotherapy for Pain Management / 5 Contact Hours	$30
☐	90240	Pancreatic Cancer / 10 Contact Hours	$60

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☐	90782	Colorectal Cancer / 15	$98
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☐	91784	Smoking and Secondhand Smoke / 10	$68
☐	94954	Osteoarthritis / 10	$68
☐	95300	Substance Use Disorders and Pain Management / 8	$56
☐	95500	Opioid Safety: Balancing Benefits and Risks / 5	$38
☐	96442	Suicide Assessment and Prevention / 6	$44
☐	96790	Psychedelic Medicine & Interventional Psychiatry / 10	$68
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☐	97000	Implicit Bias in Health Care / 3	$26
☐	98020	Commonly Abused Supplements / 2	$23
☐	98030	Getting to the Point: Acupuncture & Acupoint Therapies / 4	$32
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1. Was the course content new or review?
2. How much time did you spend on this activity?
3. Would you recommend this course to your peers?
4. Did the course content support the stated course objective?
5. Did the course content demonstrate the author's knowledge of the subject?
6. Was the course content free of bias?
7. Before completing the course, did you identify the necessity for education on the topic to improve your nursing practice?
8. Have you achieved all of the stated learning objectives of this course?
9. Has what you think or feel about this topic changed?
10. Did study questions throughout the course promote recall of learning objectives?
11. Did evidence-based practice recommendations assist in determining the validity or relevance of the information?
12. Are you more confident in your ability to provide nursing care after completing this course?
13. Do you plan to make changes in your nursing practice as a result of this course content?

#35270
Multimodal Pharmacotherapy
5 Contact Hours

1. ☐ New ☐ Review
2. ____ Hours
3. ☐ Yes ☐ No
4. ☐ Yes ☐ No
5. ☐ Yes ☐ No
6. ☐ Yes ☐ No
7. ☐ Yes ☐ No
8. ☐ Yes ☐ No
9. ☐ Yes ☐ No
10. ☐ Yes ☐ No
11. ☐ Yes ☐ No
12. ☐ Yes ☐ No
13. ☐ Yes ☐ No

#90240
Pancreatic Cancer
10 Contact Hours

1. ☐ New ☐ Review
2. ____ Hours
3. ☐ Yes ☐ No
4. ☐ Yes ☐ No
5. ☐ Yes ☐ No
6. ☐ Yes ☐ No
7. ☐ Yes ☐ No
8. ☐ Yes ☐ No
9. ☐ Yes ☐ No
10. ☐ Yes ☐ No
11. ☐ Yes ☐ No
12. ☐ Yes ☐ No
13. ☐ Yes ☐ No

#35270 Multimodal Pharmacotherapy for Pain Management — If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team? _____

_____

_____

#90240 Pancreatic Cancer — If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team? _____

_____

_____

May we contact you later regarding your comments about these activities? ☐ Yes ☐ No

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