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#96102 Frontotemporal Dementia (2 contact hours) 1
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Customer Information/Evaluation ..... Located between pages 48–49
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Course Availability List 94–96

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Published by NetCE,
a TRC Healthcare Company
P.O. Box 997571
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Frontotemporal Dementia

Includes 1 Pharmacotherapeutic/Pharmacology Hour

Audience
This course is designed for nurses, physicians, and allied health and mental health professionals who may intervene to support patients with frontotemporal dementia and their families.

Course Objective
The purpose of this course is to provide healthcare professionals with current information on frontotemporal dementia (FTD). Understanding the epidemiology, pathology, clinical features, diagnostic process, genetics, symptom treatment/management, role of brain autopsy, and current research provides a foundation for the care of patients with FTD and support for their families.

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

1. Describe the epidemiology of frontotemporal dementia (FTD) in the United States.
2. Explain the brain changes of FTD and their general clinical manifestations.
3. Identify the three general presentations of FTD.
4. Review how a clinical diagnosis of FTD is made, including differentiation from Alzheimer disease.
5. Summarize the role of genetics in FTD.
6. Discuss strategies for managing symptoms of FTD and providing support to family caregivers.
7. Identify goals of current research on FTD.

Faculty
Ellen Steinbart, RN, MA, received a Bachelor of Arts from Macalester College in 1972, a Bachelor of Science in Nursing from Cornell University-New York Hospital School of Nursing in 1974, and a Master of Arts from the University of Washington School of Nursing in 1979. She worked as a hospital medical-surgical nurse and an intensive-care burn unit nurse, and she taught medical-surgical nursing at the University of Washington School of Nursing. For 25 years, she was a research nurse at the University of Washington, coordinating research projects on the role of genetics in dementia, including frontotemporal degeneration. She is now retired.

Lauren E. Evans, MSW, received her Master's degree in Social Work from California State University, Sacramento, in 2008. Her focus was on political and community social work. She has also been a Registered International Instructor of Therapeutic Horseback Riding through the Professional Association of Therapeutic Horsemanship International (PATH Intl.) since 2006. She currently works as a mental health practitioner with the homeless population.

Faculty Disclosure

Contributing faculty, Ellen Steinbart, RN, MA, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Contributing faculty, Lauren E. Evans, MSW, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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INTRODUCTION

Frontotemporal dementia (FTD) is a group of degenerative brain disorders characterized by behavior and language problems and also overlapping with some motor/movement diseases. FTD causes progressive deterioration in a person's ability to function as the result of damage to the frontal and temporal lobes of the brain. FTD is also referred to as frontotemporal degeneration, frontotemporal lobar degeneration, and Pick disease.

Dr. Arnold Pick, a Czech neurologist, psychiatrist, and neuropathologist, first described frontal and temporal lobe atrophy causing dementia and progressive aphasia in 1892 [1]. The clinical syndrome subsequently became known as "Pick disease." FTD is the third leading cause of dementia across all age groups, after Alzheimer disease (AD) and Lewy body dementia [2]. It is one of the most common causes of early-onset dementia, with onset typically between 45 and 64 years of age [2; 3].

The clinical presentation of FTD can be complex, and obtaining an accurate diagnosis can be challenging. The unique clinical symptoms of FTD, neuropsychologic assessment, and brain imaging can help distinguish it from AD and other dementias. There is presently no effective treatment for FTD, and symptom management can be challenging for healthcare providers and family caregivers. Research is in progress to better understand FTD, hopefully leading to effective treatment, cure, and prevention of this devastating disease.

EPIDEMIOLOGY OF FTD

What is the typical age of onset of FTD?

It is estimated that FTD affects approximately 60,000 people in the United States [3]. As noted, the age of onset for FTD is typically 45 to 64 years, with a mean of 58.5 years and a reported range between 21 and 80 years of age [2; 3; 4; 5]. In the United States, the prevalence in people 45 to 64 years of age is estimated at 15 to 22 per 100,000 population; the incidence in this group is 2.7 to 4.1 per 100,000 [5]. It is estimated that 60% of those with FTD have onset between 45 and 64 years of age; 10% have onset before 45 years of age, and 30% have onset after 64 years of age [5]. FTD is now considered by some to be the most common form of pre-senile dementia in patients younger than age 60, even more common than AD in this group [6; 7; 8].

FTD affects both men and women. However, it is unclear if men and women are affected equally, or if some subtypes of FTD may be more common in one gender or the other [9]. Significant time (average: 3.6 years) often passes between symptom onset and actual clinical diagnosis [5].

The disease duration for FTD can range from 2 to 20 years from symptom onset to death, with a mean duration of 6 to 13 years [3; 5]. Pneumonia is the most common cause of death [3].

PATHOGENESIS AND PATHOPHYSIOLOGY OF FTD

Which areas of the brain are typically atrophied in patients with FTD?

Patients with FTD experience a progressive loss of neurons in the frontal and anterior temporal lobes, resulting in atrophy in these areas of the brain. They may also develop gliosis in the frontal and temporal lobes where neurons have been lost or damaged.

In FTD, affected neurons have an abnormal accumulation of protein within the cell, called inclusions. Three types of intra-neuronal inclusions have been identified, based on the protein involved. In some cases, the inclusions are composed of an abnormal form of the protein tau. In other patients, the inclusions are composed of the transactive response DNA-binding protein 43 (TDP-43). In a smaller number of FTD cases, the inclusions are composed of fused in sarcoma (FUS) protein [10].

The frontal and anterior temporal lobes of the brain control executive functions (e.g., planning, organizing, abstract thinking, judgment, decision making), personality, social behavior, and language. The changes associated with FTD causes impairments in executive function, personality, behavior, and/or language. The location of the neurodegeneration correlates fairly well with the clinical presentation [10]. Changes in other areas of the brain may cause overlapping movement problems. While the cause of most cases of FTD is not known, some cases are now known to be caused by genetic mutations.

CLINICAL PRESENTATION

What is the most common presentation of FTD?

FTD causes a gradual, progressive decline in behavior and/or language; movement disorders may also be involved. Behavior or language problems are typically the first and most prominent symptoms of FTD, whereas memory problems are the first symptoms of AD [5]. Subtypes of FTD have been identified based on clinical presentation (***Table 1***). Behavioral variant FTD (bvFTD) is the most common form and involves changes in behavior, personality, and emotions. Language presentations are referred to as primary progressive aphasia (PPA) and can take one of three forms: nonfluent/agrammatic variant PPA (nfvPPA), semantic variant PPA (svPPA), or logopenic variant PPA (lvPPA) [11].

FORMS OF FRONTOTEMPORAL DEGENERATION
Behavioral presentation • Behavioral variant FTD (bvFTD) Language presentation, variants of primary progressive aphasia (PPA) • Nonfluent/agrammatic PPA (nfvPPA), previously called progressive non-fluent aphasia (PNFA) • Semantic variant PPA (svPPA), previously called semantic dementia (SD) • Logopenic variant PPA (lvPPA) (often found to have Alzheimer disease pathology at autopsy) Associated movement disorders (not classified as FTD, but have shared symptoms) • Corticobasal syndrome (CBS) • Progressive supranuclear palsy (PSP) • Motor neuron disease, also called amyotrophic lateral sclerosis (FTD/MND or FTD/ALS)
Source: Compiled by Author *Table 1*

BEHAVIORAL VARIANT FTD	
Major Clinical Features	**Examples**
Disinhibition	Making inappropriate comments, taking food off someone else's table at a restaurant, telling sexual jokes, shoplifting, hitting
Apathy	Less involved in old hobbies or activities, deterioration in personal hygiene
Loss of empathy	Indifferent when a family member is hurt
Compulsive behaviors	Repeating the same phrase, clapping hands in the same pattern repeatedly, checking the time repeatedly
Hyper-oral behaviors	Overeating, eating one certain type of food, eating excessive sweets
Impaired executive function	Poor performance at work, poor financial decisions, difficulty planning and preparing a meal
Source: Compiled by Author	*Table 2*

Nonfluent/agrammatic PPA begins with problems in speech production, while svPPA involves impaired word comprehension and object recognition and lvPPA involves word-finding problems. A movement presentation may appear as progressive supranuclear palsy (PSP), corticobasal syndrome (CBS), or motor neuron disease (MND). Some patients may present with symptoms that overlap the different subtypes of FTD or may develop symptoms of other subtypes of FTD as the disease evolves. As more is learned about FTD, the terminology and classification of the subtypes may be revised.

BEHAVIORAL PRESENTATION

Behavioral Variant FTD

As noted, bvFTD is the most common type of FTD, estimated to account for more than half of all cases [12]. The prominent features include disinhibition, apathy/inertia, loss of empathy, compulsive behaviors, hyper-orality, and impaired executive function (***Table 2***) [13]. People with FTD may become socially withdrawn, inflexible, and impulsive. They may have a shortened attention span and a tendency to be easily distracted. Behavior may become socially inappropriate. People with bvFTD are usually unaware of the changes in their personality and behavior and the impact these changes have on others. Memory and visual-spatial functioning are initially relatively spared in bvFTD. Some individuals with bvFTD may develop symptoms similar to Parkinson disease, such as bradykinesia, rigidity, postural instability, and masked face.

LANGUAGE PRESENTATION

Nonfluent/Agrammatic Variant PPA

Nonfluent/agrammatic variant PPA, also referred to as progressive non-fluent aphasia (PNFA), accounts for about 25% of all FTD cases and involves problems with language expression [12]. People with nfvPPA have difficulty producing speech but retain the meaning of words and know what they want to say. As a result, speech may become hesitant, slow, and labored. Speech patterns may be "agrammatic" or "telegraphic," meaning that only the most important content words are used, without connecting words. For example, a patient might say "Tuesday…hospital…sister." Patients with nfvPPA have difficulty talking on the telephone and tend to talk progressively less. Eventually, some may become mute. While in the early stages, these patients continue to

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understand the speech of others, but this comprehension is eventually lost also. Reading and writing skills are better preserved than speech, although these abilities are also eventually lost. As the disease progresses, patients may develop behavioral symptoms. Some individuals with nfvPPA may develop extrapyramidal symptoms of rigidity and tremors, as seen in CBS and PSP.

Semantic Variant PPA

Semantic variant PPA, also referred to as semantic dementia, represents about 20% of FTD cases [12]. Semantic variant PPA involves the loss of understanding of the meaning of words and objects. Speech is still fluent and grammatically correct, but people with svPPA have a declining ability to comprehend the meaning of words (especially nouns) or to recognize familiar objects or faces. For example, a person with svPPA who is very familiar with vegetables might read a menu and ask: "What is broccoli?" If shown a picture of a carrot, the patient may not be able to name it and may not recognize the word when told. There are progressive word-finding problems, reading and spelling skills decline, and retrieving names becomes difficult. Later in the disease, people with svPPA may develop behavioral changes similar to those seen in patients with bvFTD.

Logopenic Variant PPA

Logopenic variant PPA is characterized by difficulty retrieving words, resulting in slow speech with frequent pauses. These patients may also have trouble repeating long phrases and understanding complex sentences. Eventually, people with lvPPA may become mute. Reading and writing skills are initially preserved, but these decline as the disease progresses. People with lvPPA have word-finding problems similar to people with AD and are often found to have AD pathology at autopsy [8].

For all patients with suspected language presentations of FTD, it is important to consider the role of culture and preferred language.

FTD OVERLAP WITH MOVEMENT DISORDERS

Progressive Supranuclear Palsy

PSP is a neurodegenerative condition characterized by problems with gait and balance, causing postural instability, falls, and difficulty with eye movement coordination. The pathophysiology of PSP shows a loss of cells in the basal ganglia, substantia nigra, subthalamus, and brainstem, and affected neurons have inclusions composed of abnormal tau protein. There are similarities between PSP and Parkinson disease, including bradykinesia, rigidity, masked face, dysarthria, dysphagia, apathy, and depression. Some people with PSP develop behavioral problems, but these are often milder than those seen in other types of FTD. Some people with PSP may develop progressive memory and language problems, and there may be a decline in executive function.

Corticobasal Syndrome

CBS is a neurodegenerative condition that may initially present with movement problems, dementia, or both. In CBS, there is atrophy in multiple areas of the brain, including the frontoparietal regions, basal ganglia, and cerebral peduncles. Neuronal inclusions are usually composed of abnormal tau protein. Signs of CBS typically begin with decreased movement on one side of the body, muscle rigidity, and tremor. A hand, arm, or leg on the affected side may demonstrate apraxia (i.e., inability to make the limb follow commands). Patients may describe the affected limb as not feeling like a part of their body, a sensation referred to as "alien limb syndrome." Symptoms may become bilateral as the disease progresses. People with CBS may also experience personality changes, executive dysfunction, and language problems as the disease progresses.

FTD with Motor Neuron Disease

Approximately 15% of people with FTD also develop problems with motor neurons that control voluntary movement [10]. This is referred to as FTD with motor neuron disease (FTD/MND) or FTD with amyotrophic lateral sclerosis (FTD/ALS). Pathologically, in addition to frontal and temporal lobe atrophy, there is also atrophy in the motor regions of the cortex and loss of motor neurons in the brain stem and spinal cord. In FTD/MND, damaged neurons usually have abnormal inclusions composed of the protein TDP-43. Patients may present with behavior or language problems, but then additionally develop muscle problems, including weakness, stiffness, twitches, cramps, and/or atrophy. Muscle problems can affect arms, legs, face, mouth, and tongue, causing patients to experience clumsiness, dysphagia, dysarthria, and hyper-reflexia. An estimated 15% of patients with MND or ALS go on to develop behavioral and executive dysfunction symptoms of FTD as their disease progresses [10].

CLINICAL DIAGNOSIS OF FTD

How do the early symptoms of FTD and Alzheimer disease differ?

The diagnosis of FTD can be challenging because of the wide range of symptoms, the relatively early age of onset, and the slow progression. There is no single test to diagnose FTD, and it may be initially misdiagnosed as a psychiatric disorder (e.g., depression, schizophrenia), AD, Parkinson disease, or vascular dementia. Accurate diagnosis of FTD is important because some of the medications used to treat these other diseases may be detrimental to patients with FTD. Patients with suspected FTD are often referred to neurologists or neuropsychologists with special expertise in FTD and related neurodegenerative disorders for a comprehensive evaluation.

The clinical diagnosis of FTD is based on the clinical history, family history, neurologic examination, neuropsychologic evaluation, and neuroimaging. Other tests may also be performed for differential diagnosis. The diagnostic process

EARLY SIGNS AND SYMPTOMS OF FTD VERSUS ALZHEIMER DISEASE		
Clinical Features	**FTD**	**Alzheimer Disease**
Hallmark	Decline in behavior, language, and/or movement; memory is retained initially	Decline in memory; socially appropriate behavior is retained initially
Initial language problems	May involve speech production, understanding words and recognizing familiar objects, or retrieving words	Word-finding or name recall
Age at onset	Usually 45 to 64 years of age	Usually 65 years of age or older
Movement problems	May have early movement disorder, with gait and balance problems, rigidity, apraxia, or muscle weakness	Usually no movement problems early in disease

Source: [3; 8; 14] *Table 3*

may take time, and the diagnosis may change as more tests are done or as new symptoms appear.

The clinical history is obtained from the patient and his/her family or friends. It is important that family or friends provide information regarding symptoms, as patients are often unaware of their behavior changes.

The family history should focus on whether any other relatives have had a neurodegenerative disease. Any cases of dementia, language problems, or movement disorders should be noted, along with specific information about symptoms, diagnosis, age of onset, course of disease, age at death, and autopsy findings. Such background information may be valuable for both diagnosis and understanding genetic risk.

The neurologic examination typically includes assessment of the patient's general appearance and speech, mental status, cranial nerves, motor system, sensation, reflexes, and cerebellar function (coordination and balance). Consulting a neurologist who has knowledge and experience in FTD can be valuable when reaching a definitive diagnosis.

The neuropsychologic examination assesses brain function and may identify areas of the brain that have been damaged. It typically involves an interview and the administration of written tests. These tests may focus on attention and concentration, memory, orientation, language, visual-spatial abilities, and/or executive functions (e.g., reasoning, planning, organizing, problem solving). Patients with FTD may show deterioration in the areas of attention and concentration, language, and executive function, but may do relatively well on memory and visual-spatial tests.

The Neuropsychiatric Inventory (NPI) may be administered to caregivers of patients with suspected FTD. This survey helps assess behavior and psychopathology by inquiring about the patient's delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability, unusual motor activity, nighttime behavioral problems, and eating abnormalities.

Brain scans are important tools in the diagnosis of FTD. Computed tomography (CT) may be done to determine if there is a tumor, hemorrhage, or other brain injury that could account for the symptoms. Magnetic resonance imaging (MRI) provides better visualization of the brain than CT and is often done to evaluate brain atrophy when FTD is suspected. Patients with FTD have progressive frontal and anterior temporal atrophy apparent on MRI. Typically, in bvFTD, there is atrophy of the frontal lobe (involved in personality, judgment, and executive function) and the anterior temporal lobe. In nfvPPA, there is left frontal lobe atrophy (involved in speech production). In svPPA, the atrophy is focused in the anterior temporal lobe (involved in language and face recognition). In specialty or research centers, positron emission tomography (PET), single photon emission computed tomography (SPECT), or functional MRI (fMRI) brain scans may be done to further evaluate brain functioning.

While there is no laboratory test that can diagnose FTD, some tests may be ordered to rule out other diseases with symptoms similar to those of FTD. Blood work may be ordered to identify dehydration, thyroid disease, vitamin B12 deficiency, or infections affecting the brain. An electroencephalogram (EEG) may be done if there is concern that seizures might be causing the patient's symptoms. In the early stages of FTD, EEG findings are usually normal or have non-specific findings. Lumbar puncture may be done to evaluate cerebral spinal fluid and rule out rare brain infections or cancer. Electromyography may be used to identify muscle weakness or myoclonus if MND (or ALS) is being considered as a possible diagnosis. In addition, language evaluation by a speech pathologist can be an important tool in diagnosing patients with nonfluent/agrammatic, semantic, or logopenic variant PPA.

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It may be challenging to clinically differentiate FTD from early AD (***Table 3***). The only way to establish an unquestionable diagnosis of FTD is through a brain autopsy after a patient has died. Examination of the brain tissue will show the precise location and severity of the brain atrophy, and microscopic studies can determine the protein composition of the inclusions in affected neurons.

For families, brain autopsy can confirm the diagnosis (or identify a different cause of the dementia) and bring a measure of closure. Accurate diagnosis may be especially important if there is concern about genetic risk to other family members.

Discussion about brain autopsy should be handled delicately and with compassion at a time that is appropriate for the family; the subject may be emotionally difficult for some families. Introducing the topic ahead of time allows families to consider their feelings about brain autopsy aside from the emotional crisis of the death of a loved one and the immediate time pressure of funeral arrangements. Families may then discuss the topic among themselves and come to a consensus.

Should a family wish to have a brain autopsy done when the patient dies, the physician can help identify a pathology service experienced in neurologic disorders and preliminary logistical planning can be done ahead of time. Arrangements may be coordinated with a research center that specializes in brain autopsy for FTD. The autopsy is done as soon as possible after death, often within 6 to 24 hours. The procedure is not disfiguring, so open-casket funerals may be planned if the family so chooses.

In addition to answering families' questions regarding diagnosis, brain autopsy can also aid researchers in better understanding the correlation between the clinical signs of FTD and the pathologic changes in the brain. This may benefit future generations by improving diagnosis and advancing research on therapies for FTD.

GENETICS AND FTD

If a parent carries a genetic mutation in the *MAPT* gene causing FTD, what is the risk to his/her child of inheriting the same genetic mutation?

Understanding of the role of genetics in FTD is still evolving. Presently, it appears that most cases of FTD (approximately 60%) are sporadic, meaning one person in a family has the disease, there is no family history of any relative with the disease, and the disease does not appear to be inherited.

However, approximately 40% of those with FTD report a family history of one or more relatives with a neurodegenerative disease [6; 9; 10]. This is referred to as familial FTD. In some cases of familial FTD, no specific genetic mutation can be identified as the cause. The risk to family members of a person with familial FTD without an identified genetic mutation is increased over the general population, but the specific increased risk is unclear.

An estimated 10% to 20% of all FTD cases are caused by an inherited genetic mutation [6; 8]. Patients with a strong family history of multiple relatives with FTD and/or MND are more likely to have an inherited form of FTD caused by a genetic mutation. Genetic mutations causing FTD are inherited in an autosomal dominant inheritance pattern, meaning each child of an affected parent is born with a 50% chance of inheriting the genetic mutation.

Several specific genetic mutations have been identified as being implicated in inherited FTD. In 1998, the first gene associated with hereditary FTD—the microtubule-associated protein tau (*MAPT*) gene on chromosome 17—was discovered [15; 16]. Mutations in this gene cause an abnormal accumulation of tau protein in affected neurons. *MAPT* mutations are thought to account for 2% to 11% of familial FTD cases [17]. These mutations most commonly cause bvFTD but may also cause svPPA, PSP, and/or CBS. FTD symptoms may vary widely, even within families.

In 2006, mutations in the progranulin (*GRN*) gene on chromosome 17 were discovered to cause FTD [18; 19]. Mutations in the *GRN* gene cause abnormal accumulations of TDP-43 protein in affected neurons. *GRN* mutations are thought to represent about 5% to 10% of all inherited FTD cases [17]. They most commonly cause bvFTD, but are also associated with nfvPPA and CBS. *GRN* mutations appear to have decreased penetrance, meaning that, for unknown reasons, some people with the mutation may not develop symptoms of the disease.

In 2011, the genetic mutation *C9orf72* was discovered on chromosome 9 [20; 21]. Mutations in *C9orf72* cause an abnormal accumulation of TDP-43 in affected neurons. To date, *C9orf72* mutations are the most common genetic cause of FTD, found in about 25% of familial FTD and 6% of sporadic cases [22]. *C9orf72* mutations appear to cause FTD (usually bvFTD or language presentation), MND, and a combination of FTD and MND.

Other very rare genetic mutations have also been associated with FTD. Mutations in the gene valosin-containing protein (VCP) on chromosome 9, charged multivesicular body protein 2B (CHMP2B) on chromosome 3, TAR DNA-binding protein (TARDBP), FUS, TBK1, EXT2, and SQSTM1 have been associated with FTD [29].

Clinical genetic testing is available for the *MAPT*, *GRN*, and *C9orf72* genetic mutations causing hereditary FTD, as well as some of the other very rare genetic mutations. Genetic testing may be ordered after informed consent and clear discussion of the implications with the patient and his/her family. For patients with FTD, identification of a genetic mutation confirms the diagnosis of FTD and provides information about

risk to other family members. Each of the patient's siblings and each of the patient's children would be at 50/50 risk for having inherited the genetic mutation causing FTD. If a genetic mutation causing FTD is identified, other at-risk family members may be tested.

If a genetic mutation causing FTD is identified in a patient with FTD, unaffected at-risk family members could choose to have pre-symptomatic (predictive) genetic testing done to determine if they have inherited the genetic mutation that would someday cause FTD. Individuals considering pre-symptomatic genetic testing are referred for formal professional genetic counseling to help them make the best decision regarding whether or not to learn their FTD genetic status.

MANAGEMENT OF FTD

Which medications are approved for the treatment of FTD?

There is presently no treatment to slow the progression of or cure FTD. No medication has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of FTD; however, medications used to treat other disorders may be prescribed off-label for the management of FTD symptoms. Their use may be limited by the potential adverse effects. Antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), may be prescribed for behavioral symptoms of FTD, and low-dose trazodone has been used for agitation and aggression [9]. While the anticholinesterase inhibitors donepezil, galantamine, and rivastigmine are beneficial for some patients with AD, they generally have not been helpful for patients with FTD [9]. The glutamate NMDA receptor antagonist memantine, used for moderate-to-severe AD, has been used for patients with FTD as well, but a 2013 study showed that it provided no benefit to patients with FTD and that it may be harmful to cognition [23]. Antipsychotics are occasionally used to treat significant agitation and behavioral symptoms, but only with caution, as antipsychotics can have serious adverse effects such as extrapyramidal adverse effects (parkinsonism), depression, sedation, falls, incontinence, and disinhibition, and patients with FTD may have an increased susceptibility to the these effects [9]. Elderly patients with dementia who take antipsychotics have a 1.6- to 1.7-fold increase in mortality secondary to cardiac problems or infection, prompting the FDA to issue a warning about their use in older patients with behavioral disturbances [9]. L-DOPA has shown a minimal response for parkinsonism in patients with PSP and CBD [28]. Research is being done to further evaluate the use of available medications for the management of FTD and to find new, more effective treatments.

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the Royal Australian and New Zealand College of Psychiatrists, general principles of dementia care apply for the management of frontotemporal dementia, but specific issues relate to the early onset of the illness in middle life and that affected persons may lack insight into their deficits leading to occupational and social problems.

(https://journals.sagepub.com/doi/abs/10.1177/1039856215582276. Last accessed October 15, 2021.)

Strength of Recommendation/Level of Evidence: Expert Opinion/Consensus Statement

Management of FTD includes providing care to patients with FTD and support to their families. Caring for a person with FTD involves managing the symptoms, keeping the patient safe, and providing help in activities of daily living.

Apathy is a common symptom in patients with bvFTD, often resulting in neglect of their personal hygiene and grooming. Supervision, encouragement, and help with bathing, dressing, and grooming may be needed. For behavioral problems, simple interventions like distraction (e.g., introducing a new activity) may help interrupt the troublesome behavior. For some patients, modification of the environment or behavior may help minimize the potential for harm. For example, if the patient is pacing, creating a safe route for him or her to walk can be helpful. Physical therapists may be able to help develop an exercise program to maintain mobility. Exercise has also been shown to improve mood and cognition and may improve behavior management in patients with dementia [24]. If behaviors such as agitation or aggression become severe, a medication may be prescribed off-label to control difficult or dangerous behaviors. Supervision may be necessary to ensure patients take medications as prescribed.

Some individuals with FTD have eating problems, such as overeating, eating just one type of food, or craving sweets. For these patients, it may be necessary to monitor weight and provide help with meal preparation to provide a balanced, nutritious diet. Access to additional foods, drinks, or sweets should be limited.

Speech pathologists or therapists may be helpful in diagnosing the specific language problems exhibited by patients with FTD, including nonfluent/agrammatic, semantic, or logopenic variant PPA. Speech therapy may also help patients to find new communication strategies, such as sign language, carrying cards with specific messages, or using a computer with pre-programmed words or phrases [25]. Such techniques may help those with language problems communicate with family and friends. Speech therapists may also be able to evaluate and address swallowing problems, if these arise.

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Caring for a patient with FTD includes maintaining a safe environment for the patient and for those around him/her. A structured environment and keeping the daily routine the same is often helpful. In addition, persons with FTD should no longer drive, and safety measures should be taken at home, especially in the kitchen and bathroom. If a patient with FTD shows aggression, disinhibition, or poor judgment, close supervision is necessary when he/she is around others, especially children or the frail elderly, to prevent them from being inadvertently harmed.

It also may be necessary to monitor the patient's behavior in public places. If an individual displays inappropriate behavior, tense situations may be diffused by explaining that he or she has FTD and cannot control his/her behavior. Simple cards with this brief explanation can be made, carried, and shared with people who might be disturbed by a patient's inappropriate behavior.

If a patient with FTD has gait and balance problems, measures should be taken to prevent falls. This may include keeping the home environment free of obstacles and loose rugs and installing shower bars and a raised toilet seat. Mobility aids may be helpful. Occupational therapists should provide intervention to help patients with FTD complete activities of daily living as the disease progresses.

CAREGIVER SUPPORT

FTD places enormous burdens on the family. Most dementia care is provided at home by family caregivers, often spouses. Caregivers for those with FTD face physical, emotional, and financial challenges. FTD caregiver burden, stress, and depression are greater even than that seen with AD [26; 27].

The first challenge that families of those with FTD may face is obtaining an accurate diagnosis. The process can involve years of uncertainty and stress before the correct clinical diagnosis of FTD is made. Even during the diagnosis process, support for families begins with information and education about FTD. Accurate information can lead to understanding and a greater sense of control over the stressful situation. It is important for families and caregivers to understand that the behavior changes they observe are the result of the disease. Their loved one may display behaviors that are embarrassing, offensive, self-centered, uncaring, and aggressive, with complete lack of insight about how the behavior affects others. The caregiver may feel like he/she is suddenly living with a stranger.

The aggression, disinhibition, and poor judgment associated with FTD can put family members at risk of harm. Because FTD affects people at a relatively young age, there may still be children in the home. Families should recognize the risk to others in the home and seek help creating strategies to keep themselves and other family members safe.

Language may be impaired in people with FTD, making communication difficult. This can interfere not only with communication between the patient and the caregiver, but it can also limit participation in larger social activities. Speech therapy can provide new approaches to communication, helping not only the patient but also the caregiver.

Because FTD usually begins at a relatively young age, it can cause a significant financial burden for families. There may be loss of income, and retirement benefits may be affected because the patient is unable to continue working. Financial and legal issues that should be addressed include insurance, social security disability, financial planning for the future (when additional care will be needed), power-of-attorney arrangements, and a living will. Social workers, financial advisors, and attorneys are resources available to families to help address these issues.

The demands on caregivers increase as FTD progresses. Caregivers will be required to provide more supervision and increasing assistance for activities of daily living. While providing care for an individual with FTD, the caregiver may also be grieving the loss of his or her previously healthy loved one. Family caregivers can become physically and emotionally exhausted, and they may feel isolated in their role as caregiver. Interventions to help reduce caregiver stress include an individualized patient management plan, environmental changes to promote safety and facilitate care, and strengthening caregiver coping strategies and skills. Family caregivers should be encouraged to ask for and accept help in caring for their loved one with FTD, allowing them to take time for themselves and address their own health needs. Connection with community resources may also be helpful. Community resources for FTD caregivers include national organizations such as the Association for Frontotemporal Degeneration, attorneys and financial planners, social service programs, adult day care programs, respite care, support groups, and individual or family counseling.

Family caregivers should look ahead and consider how they wish care to be provided to their loved one as FTD progresses. Patients with FTD will become more dependent and more difficult to safely manage at home by a family caregiver as the disease progresses. Social workers can be a good resource to caregivers as they consider options such as extra in-home nursing care, care communities, and long-term care facilities. Locating an appropriate care facility that accepts patients with FTD can be challenging. These patients are often younger, stronger, and more active than the typical residents of care facilities. Facility staff may need education and support to understand the unique features of FTD and to learn how to provide care to these patients while maintaining a safe environment for all residents in the facility.

Nurses play an important role in caring for those with FTD and providing support to their families. Nurses interact with patients with FTD and their families in the outpatient clinic setting, in-home care setting, and long-term care facility and may be involved in monitoring symptoms, developing and implementing individualized patient care plans, and providing direct patient care. It is important for all healthcare providers to coordinate care for the patient with FTD. All members of the interdisciplinary healthcare team can support families by listening to them, providing ongoing information and education about FTD, offering guidance to improve caregiving skills, and helping families connect to appropriate resources.

PROGRESSION OF FTD

The prognosis for people with FTD is poor. FTD worsens progressively, usually over several years, and patients require increasing behavioral supervision and personal care. Eventually, people with advanced FTD become mute and bedbound and require full care at home or in a care facility. As patients with FTD become more debilitated, they are vulnerable to complications such as infections and falls. The most common cause of death in people with FTD is infection (e.g., pneumonia) [3; 8]. The average duration of the disease is 6 to 13 years, but it can range from 2 to 20 years [3; 5].

RESEARCH RELATED TO FTD

What are the goals of research on FTD?

The goals for research on FTD include gaining a better understanding of the pathology; identifying causes and risk factors (genetic and environmental); improving the diagnosis of FTD through enhanced neuroimaging, biomarkers, and characterization of clinical features; developing therapies to treat, cure, or prevent FTD; and exploring new ways to support family caregivers. However, research on FTD is challenging. It is an uncommon disease, so awareness is low, there are fewer potential subjects available for research studies, and there is a relatively small market for medications. FTD is a complicated disease with a wide variety of presentations (behavior, language, and movement problems) and underlying causes (sporadic and genetic). Pathologically, microscopic brain inclusions may consist of different abnormal proteins (e.g., tau, TDP-43, FUS), but there are no good biomarkers to diagnose FTD or to monitor the progression of the disease. Drug development faces the challenge of creating a medication to treat FTD that can cross the blood/brain barrier.

Despite these challenges, the pace of research on FTD has accelerated rapidly. There are an increasing number of studies and a better awareness of the varied symptoms of FTD. In the past few decades, there have been discoveries of the genetic mutations underlying some causes of FTD and a growing understanding of the changes that occur in the brain of those with FTD. Presently, there are clinical trials underway for potential medications to treat FTD. Information on clinical research studies, including participation in studies, can be found at the National Institutes of Health website https://clinicaltrials.gov.

CASE STUDY

Patient A was a high school homecoming queen who completed two years of college, worked in an office, then married and had three children. She was an energetic homemaker and an active community volunteer, serving as school parent-teacher association president for several years, and was fastidious about her appearance.

Patient A's mother, three maternal uncles, a maternal grandfather, and great-grandmother died with dementia; her brother and maternal aunt are living with the disease. The mean age of onset of dementia in the family is 51 years, and the mean age at death is 67 years.

When Patient A is 52 years of age, her husband notices changes in her behavior. She often appears distracted, and her impeccable grooming declines. She is less affectionate toward him and she stops participating in community activities. She has difficulty making arrangements for a planned vacation. Her previously gourmet meals become simple, functional meals. She becomes obsessed with repeatedly raking the lawn, eventually killing all the grass in the yard. When her grandchildren visit, Patient A alternates between ignoring them and playing too rough. Patient A begins to impulsively leave the house for fast-paced walks, but she always returns home and never gets lost. She frequently visits a local shopping mall, getting down on her hands and knees looking for dropped change near the cash registers. She is once stopped by mall security for shoplifting. When shopping with her husband, she approaches strangers, stands inappropriately close to them, and announces "We don't know you."

Patient A's husband brings her to a dementia clinic for evaluation. A neurologic examination and neuropsychologic testing are completed. Memory and visual-spatial performance are in the normal range, but personality, judgment, and executive function show significant decline. A brain MRI shows frontal and anterior temporal lobe atrophy, and the diagnosis of familial bvFTD is made. Clinical genetic testing identifies a mutation in the *MAPT* gene on chromosome 17, the believed cause of the dementia.

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Patient A's husband stops working in order to care for her at home. As her disease progresses, Patient A requires increasing care and supervision. She spends much of her day watching television, writing numbers in a notebook, and pacing. She develops a craving for sweets and often rummages through kitchen cabinets looking for candy. At mealtime, Patient A stuffs her mouth with food before chewing and swallowing properly, precipitating episodes of choking. She also develops a pattern of hand-clapping that she repeats every few minutes, along with the phrase "We haven't had any phone calls lately."

Patient A's husband is encouraged to accept help from others (such as their adult children), consider local adult day care programs, and utilize respite care at a nearby nursing home. He is in monthly phone contact with nursing staff to review symptoms and develop strategies for managing symptoms. At different times during her illness, Patient A is prescribed an antidepressant and an antipsychotic medication (off label) to treat difficult behavioral symptoms, but both were eventually discontinued. The family faces financial difficulties as a result of the husband's loss of income, diminished retirement benefits, and the later cost of nursing home care. Social work support helps the family address issues such as insurance, social security benefits, adult day care programs, and selecting a nursing facility for eventual long-term care.

When Patient A is 60 years of age, her husband is no longer able to care for her at home and she is admitted to a skilled nursing facility. She is incontinent and requires full care for all activities of daily living. Her husband visits twice daily, and she always appears to recognize him. That same year, Patient A dies unexpectedly of a myocardial infarction. A brain autopsy is done and confirms the diagnosis of FTD.

Patient A's husband shares the results of her genetic testing and autopsy with their three adult children. Each of Patient A's three children is at a 50% risk for having inherited the *MAPT* genetic mutation. Two of the children request pre-symptomatic genetic testing. The two children who request pre-symptomatic genetic testing are referred to professional genetic counselors. After genetic counseling, they both choose to have pre-symptomatic genetic testing done. One defers getting the results for two years, underscoring the very difficult personal decision it can be to choose pre-symptomatic genetic testing.

Patient A demonstrated the typical symptoms of bvFTD and her evaluation was done at a dementia center by specialists with expertise in FTD, so her initial diagnosis was strong. The neurologic evaluation, blood tests, neuropsychologic testing, and neuroimaging together led to the clinical diagnosis of bvFTD. Patient A's family history showed a pattern of autosomal dominant inheritance. The genetic cause of her FTD was confirmed by clinical genetic testing, which documented a mutation in the *MAPT* gene.

CONCLUSION

FTD is now recognized as one of the most common causes of dementia in persons younger than 65 years of age. This course has provided an overview of FTD epidemiology, pathophysiology, clinical presentation, diagnosis, management, prognosis, and current research. Understanding FTD can help healthcare professionals provide better care to patients with FTD and support to their families.

RESOURCES

Association for Frontotemporal Degeneration
2700 Horizon Drive, Suite 120
King of Prussia, PA 19406
(866) 507-7222
https://www.theaftd.org

National Institute on Aging
Building 31, Room 5C27
31 Center Drive, MSC 2292
Bethesda, MD 20892-2292
(800) 222-2225
https://www.nia.nih.gov

National Institute of Neurological Disorders and Stroke
P.O. Box 5801
Bethesda, MD 20824
(800) 352-9424
https://www.ninds.nih.gov

Customer Information/Evaluation insert located between pages 48–49.

Implicit Bias in Health Care

This course meets the Michigan requirement for implicit bias training.

Audience
This course is designed for the interprofessional healthcare team and professions working in all practice settings.

Course Objective
The purpose of this course is to provide healthcare professionals with an overview of the impact of implicit biases on clinical interactions and decision making.

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

1. Define implicit and explicit biases and related terminology.
2. Evaluate the strengths and limitations of the Implicit Association Test.
3. Describe how different theories explain the nature of implicit biases, and outline the consequences of implicit biases.
4. Discuss strategies to raise awareness of and mitigate or eliminate one's implicit biases.

Faculty
Alice Yick Flanagan, PhD, MSW, received her Master's in Social Work from Columbia University, School of Social Work. She has clinical experience in mental health in correctional settings, psychiatric hospitals, and community health centers. In 1997, she received her PhD from UCLA, School of Public Policy and Social Research. Dr. Yick Flanagan completed a year-long post-doctoral fellowship at Hunter College, School of Social Work in 1999. In that year she taught the course Research Methods and Violence Against Women to Masters degree students, as well as conducting qualitative research studies on death and dying in Chinese American families. (A complete biography appears at the end of this course.)

Faculty Disclosure
Contributing faculty, Alice Yick Flanagan, PhD, MSW, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Division Planner
Jane C. Norman, RN, MSN, CNE, PhD

Division Planner Disclosure
The division planner has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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AACN Synergy CERP Category B.

Individual State Nursing Approvals
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Special Approvals
This course meets the Michigan requirement for implicit bias training.

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This course represents an educational model that promotes the importance of learning objectives and individualized learning. Study questions will appear throughout the course to create a link between the learning objectives and the supporting text.

INTRODUCTION

In the 1990s, social psychologists Dr. Mahzarin Banaji and Dr. Tony Greenwald introduced the concept of implicit bias and developed the Implicit Association Test (IAT) as a measure. In 2003, the Institute of Medicine published the report *Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care* highlighting the role of health professionals' implicit biases in the development of health disparities [1]. The phenomenon of implicit bias is premised on the assumption that while well-meaning individuals may deny prejudicial beliefs, these implicit biases negatively affect their clinical communications, interactions, and diagnostic and treatment decision-making [2; 3].

One explanation is that implicit biases are a heuristic, or a cognitive or mental shortcut. Heuristics offer individuals general rules to apply to situations in which there is limited, conflicting, or unclear information. Use of a heuristic results in a quick judgment based on fragments of memory and knowledge, and therefore, the decisions made may be erroneous. If the thinking patterns are flawed, negative attitudes can reinforce stereotypes [4]. In health contexts, this is problematic because clinical judgments can be biased and adversely affect health outcomes. The Joint Commission provides the following example [3]: A group of physicians congregate to examine a child's x-rays but has not been able to reach a diagnostic consensus. Another physician with no knowledge of the case is passing by, sees the x-rays, and says "Cystic fibrosis." The group of physicians was aware that the child is African American and had dismissed cystic fibrosis because it is less common among Black children than White children.

The purpose of this course is to provide health professionals an overview of implicit bias. This includes an exploration of definitions of implicit and explicit bias. The nature and dynamics of implicit biases and how they can affect health outcomes will be discussed. Finally, because implicit biases are unconscious, strategies will be reviewed to assist in raising professionals' awareness of and interventions to reduce them.

DEFINITIONS OF IMPLICIT BIAS AND OTHER TERMINOLOGIES

IMPLICIT VS. EXPLICIT BIAS

In a sociocultural context, biases are generally defined as negative evaluations of a particular social group relative to another group. Explicit biases are conscious, whereby an individual is fully aware of his/her attitudes and there may be intentional behaviors related to these attitudes [5]. For example, an individual may openly endorse a belief that

women are weak and men are strong. This bias is fully conscious and is made explicitly known. The individual's ideas may then be reflected in his/her work as a manager.

FitzGerald and Hurst assert that there are cases in which implicit cognitive processes are involved in biases and conscious availability, controllability, and mental resources are not [6]. The term "implicit bias" refers to the unconscious attitudes and evaluations held by individuals. These individuals do not necessarily endorse the bias, but the embedded beliefs/attitudes can negatively affect their behaviors [2; 7; 8; 9]. Some have asserted that the cognitive processes that dictate implicit and explicit biases are separate and independent [9].

Implicit biases can start as early as 3 years of age. As children age, they may begin to become more egalitarian in what they explicitly endorse, but their implicit biases may not necessarily change in accordance to these outward expressions [10]. Because implicit biases occur on the subconscious or unconscious level, particular social attributes (e.g., skin color) can quietly and insidiously affect perceptions and behaviors [11]. According to Georgetown University's National Center on Cultural Competency, social characteristics that can trigger implicit biases include [12]:

- Age
- Disability
- Education
- English language proficiency and fluency
- Ethnicity
- Health status
- Disease/diagnosis (e.g., HIV/AIDS)
- Insurance
- Obesity
- Race
- Socioeconomic status
- Sexual orientation, gender identity, or gender expression
- Skin tone
- Substance use

An alternative way of conceptualizing implicit bias is that an unconscious evaluation is only negative if it has further adverse consequences on a group that is already disadvantaged or produces inequities [6; 13]. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages [13].

When the concept of implicit bias was introduced in the 1990s, it was thought that implicit biases could be directly linked to behavior. Despite the decades of empirical research, many questions, controversies, and debates remain about the dynamics and pathways of implicit biases [2].

OTHER COMMON TERMINOLOGIES

In addition to understanding implicit and explicit bias, there is additional terminology related to these concepts that requires specific definition.

Cultural Competence

Cultural competence is broadly defined as practitioners' knowledge of and ability to apply cultural information and appreciation of a different group's cultural and belief systems to their work [14]. It is a dynamic process, meaning that there is no endpoint to the journey to becoming culturally aware, sensitive, and competent. Some have argued that cultural curiosity is a vital aspect of this approach.

Cultural Humility

What is cultural humility?

Cultural humility refers to an attitude of humbleness, acknowledging one's limitations in the cultural knowledge of groups. Practitioners who apply cultural humility readily concede that they are not experts in others' cultures and that there are aspects of culture and social experiences that they do not know. From this perspective, patients are considered teachers of the cultural norms, beliefs, and value systems of their group, while practitioners are the learners [15]. Cultural humility is a lifelong process involving reflexivity, self-evaluation, and self-critique [16].

Discrimination

Discrimination has traditionally been viewed as the outcome of prejudice [17]. It encompasses overt or hidden actions, behaviors, or practices of members in a dominant group against members of a subordinate group [18]. Discrimination has also been further categorized as lifetime discrimination, which consists of major discreet discriminatory events, or everyday discrimination, which is subtle, continual, and part of day-to-day life and can have a cumulate effect on individuals [19].

Diversity

Diversity "encompasses differences in and among societal groups based on race, ethnicity, gender, age, physical/mental abilities, religion, sexual orientation, and other distinguishing characteristics" [20]. Diversity is often conceptualized into singular dimensions as opposed to multiple and intersecting diversity factors [21].

Intersectionality

Intersectionality is a term to describe the multiple facets of identity, including race, gender, sexual orientation, religion, sex, and age. These facets are not mutually exclusive, and the meanings that are ascribed to these identities are interrelated and interact to create a whole [22].

Prejudice

Prejudice is a generally negative feeling, attitude, or stereotype against members of a group [23]. It is important not to

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equate prejudice and racism, although the two concepts are related. All humans have prejudices, but not all individuals are racist. The popular definition is that "prejudice plus power equals racism" [23]. Prejudice stems from the process of ascribing every member of a group with the same attribute [24].

Race

Race is linked to biology. Race is partially defined by physical markers (e.g., skin or hair color) and is generally used as a mechanism for classification [25]. It does not refer to cultural institutions or patterns. In modern history, skin color has been used to classify people and to imply that there are distinct biologic differences within human populations [26]. Historically, the U.S. Census has defined race according to ancestry and blood quantum; today, it is based on self-classification [26].

There are scholars who assert that race is socially constructed without any biological component [27]. For example, racial characteristics are also assigned based on differential power and privilege, lending to different statuses among groups [28].

Racism

Racism is the "systematic subordination of members of targeted racial groups who have relatively little social power…by members of the agent racial group who have relatively more social power" [29]. Racism is perpetuated and reinforced by social values, norms, and institutions.

There is some controversy regarding whether unconscious (implicit) racism exists. Experts assert that images embedded in our unconscious are the result of socialization and personal observations, and negative attributes may be unconsciously applied to racial minority groups [30]. These implicit attributes affect individuals' thoughts and behaviors without a conscious awareness.

Structural racism refers to the laws, policies, and institutional norms and ideologies that systematically reinforce inequities resulting in differential access to services such as health care, education, employment, and housing for racial and ethnic minorities [31; 32].

MEASUREMENT OF IMPLICIT BIAS: A FOCUS ON THE IAT

What tool is used to quantitatively measure implicit bias?

Project Implicit is a research project sponsored by Harvard University and devoted to the study and monitoring of implicit biases. It houses the Implicit Association Test (IAT), which is one of the most widely utilized standardized instruments to measure implicit biases. The IAT is based on the premise that implicit bias is an objective and discreet phenomenon that can be measured in a quantitative manner. Developed and first introduced in 1998, it is an online test that assesses implicit bias by measuring how quickly people make associations between targeted categories with a list of adjectives [33]. For example, research participants might be assessed for their implicit biases by seeing how rapidly they make evaluations among the two groups/categories career/family and male/female. Participants tend to more easily affiliate terms for which they hold implicit or explicit biases. So, unconscious biases are measured by how quickly research participants respond to stereotypical pairings (e.g., career/male and family/female). The larger the difference between the individual's performance between the two groups, the stronger the degree of bias [34; 35]. Since 2006, more than 4.6 million individuals have taken the IAT, and results indicate that the general population holds implicit biases [3].

interactive activity

Visit https://implicit.harvard.edu/implicit and complete an assessment. Does it reflect your perception of your own biases? Did you learn anything about yourself?

Measuring implicit bias is complex, because it requires an instrument that is able to access underlying unconscious processes. While many of the studies on implicit biases have employed the IAT, there are other measures available. They fall into three general categories: the IAT and its variants, priming methods, and miscellaneous measures, such as self-report, role-playing, and computer mouse movements [36]. This course will focus on the IAT, as it is the most commonly employed instrument.

The IAT is not without controversy. One of the debates involves whether IAT scores focus on a cognitive state or if they reflect a personality trait. If it is the latter, the IAT's value as a diagnostic screening tool is diminished [37]. There is also concern with its validity in specific arenas, including jury selection and hiring [37]. Some also maintain that the IAT is sensitive to social context and may not accurately predict behavior [37]. Essentially, a high IAT score reflecting implicit biases does not necessarily link to discriminating behaviors, and correlation should not imply causation. A meta-analysis involving 87,418 research participants found no evidence that changes in implicit biases affected explicit behaviors [38].

EXTENT OF IMPLICIT BIASES AND RISK FACTORS

Among the more than 4 million participants who have completed the IAT, individuals generally exhibited implicit preference for White faces over Black or Asian faces. They also held biases for light skin over dark skin, heterosexual over gender and sexual minorities (LGBTQ+), and young over old [39]. The Pew Research Center also conducted an exploratory study on implicit biases, focusing on the extent

to which individuals adhered to implicit racial biases [40]. A total of 2,517 IATs were completed and used for the analysis. Almost 75% of the respondents exhibited some level of implicit racial biases. Only 20% to 30% did not exhibit or showed very little implicit bias against the minority racial groups tested. Approximately half of all single-race White individuals displayed an implicit preference for White faces over Black faces. For single-race Black individuals, 45% had implicit preference for their own group. For biracial White/Black adults, 23% were neutral. In addition, 22% of biracial White/Asian participants had no or minimal implicit racial biases. However, 42% of the White/Black biracial adults leaned toward a pro-White bias.

In another interesting field experiment, although not specifically examining implicit bias, resumes with names commonly associated with African American or White candidates were submitted to hiring officers [41]. Researchers found that resumes with White-sounding names were 50% more likely to receive callbacks than resumes with African American-sounding names [41]. The underlying causes of this gap were not explored.

Implicit bias related to sex and gender is also significant. A survey of emergency medicine and obstetrics/gynecology residency programs in the United States sought to examine the relationship between biases related to perceptions of leadership and gender [42]. In general, residents in both programs (regardless of gender) tended to favor men as leaders. Male residents had greater implicit biases compared with their female counterparts.

Other forms of implicit bias can affect the provision of health and mental health care. One online survey examining anti-fat biases was provided to 4,732 first-year medical students [43]. Respondents completed the IAT, two measures of explicit bias, and an anti-fat attitudes instrument. Nearly 75% of the respondents were found to hold implicit anti-fat biases. Interestingly, these biases were comparable to the scope of implicit racial biases. Male sex, non-Black race, and lower body mass index (BMI) predicted holding these implicit biases.

Certain conditions or environmental risk factors are associated with an increased risk for certain implicit biases, including [44; 45]:

- Stressful emotional states (e.g., anger, frustration)
- Uncertainty
- Low-effort cognitive processing
- Time pressure
- Lack of feedback
- Feeling behind with work
- Lack of guidance
- Long hours
- Overcrowding
- High-crises environments
- Mentally taxing tasks
- Juggling competing tasks

THEORETIC EXPLANATIONS AND CONTROVERSIES

A variety of theoretical frameworks have been used to explore the causes, nature, and dynamics of implicit biases. Each of the theories is described in depth, with space given to explore controversies and debates about the etiology of implicit bias.

SOCIAL PSYCHOLOGICAL AND COGNITIVE THEORETICAL FRAMEWORKS

One of the main goals of social psychology is to understand how attitudes and belief structures influence behaviors. Based on frameworks from both social and cognitive psychology, many theoretical frameworks used to explain implicit bias revolve around the concept of social cognition. One branch of cognitive theory focuses on the role of implicit or nondeclarative memory. Experts believe that this type of memory allows certain behaviors to be performed with very little conscious awareness or active thought. Examples include tooth brushing, tying shoelaces, and even driving. To take this concept one step farther, implicit memories may also underlie social attitudes and stereotype attributions [46]. This is referred to as implicit social cognition. From this perspective, implicit biases are automatic expressions based on belonging to certain social groups [47]. The IAT is premised on the role of implicit memory and past experiences in predicting behavior without explicit memory triggering [48].

Another branch of cognitive theory used to describe implicit biases involves heuristics. When quick decisions are required under conditions of uncertainty or fatigue, and/or when there is a tremendous amount of information to assimilate without sufficient time to process, decision-makers resort to heuristics [49]. Heuristics are essentially mental short cuts that facilitate (usually unconscious) rules that promote automatic processing [50]. However, these rules can also be influenced by socialization factors, which could then affect any unconscious or latent cognitive associations about power, advantage, and privilege. Family, friends, media, school, religion, and other social institutions all play a role in developing and perpetuating implicit and explicit stereotypes, and cognitive evaluations can be primed or triggered by an environmental cue or experience [51]. When a heuristic is activated, an implicit memory or bias may be triggered simultaneously [47]. This is also known as the dual-process model of information processing [50].

BEHAVIORAL OR FUNCTIONAL PERSPECTIVES

Behavioral or functional theorists argue that implicit bias is not necessarily a latent or unconscious cognitive structure. Instead, this perspective recognizes implicit bias as a group-based behavior [52]. Behavior is biased if it is influenced by

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social cues indicating the social group to which someone belongs [52]. Social cues can occur rapidly and unintentionally, which ultimately leads to automatic or implicit effects on behavior. The appeal of a behavioral or functional approach to implicit bias is that it is amoral; that is, it is value- and judgment-free [52]. Rather than viewing implicit bias as an invisible force (i.e., unconscious cognitive structure), it is considered a normal behavior [53].

NEUROSCIENTIFIC PERSPECTIVES

Implicit bias has neuroscientific roots as well and has been linked to functions of the amygdala [2; 54]. The amygdala is located in the temporal lobe of the brain, and it communicates with the hypothalamus and plays a large role in memory. When situations are emotionally charged, the amygdala is activated and connects the event to memory, which is why individuals tend to have better recall of emotional events. This area of the brain is also implicated in processing fear. Neuroscientific studies on implicit biases typically use functional magnetic resonance imaging (fMRI) to visualize amygdala activation during specific behaviors or events. In experimental studies, when White research subjects were shown photos of Black faces, their amygdala appeared to be more activated compared to when they viewed White faces [55]. This trend toward greater activation when exposed to view the faces of persons whose race differs from the viewer starts in adolescence and appears to increase with age [54]. This speaks to the role of socialization in the developmental process [54].

It may be that the activation of the amygdala is an evolutionary threat response to an outgroup [56]. Another potential explanation is that the activation of the amygdala is due to the fear of appearing prejudiced to others who will disapprove of the bias [56]. The neuroscientific perspective of implicit bias is controversial. While initial empirical studies appear to link implicit bias to amygdala activation, many researchers argue this relationship is too simplistic [2].

STRUCTURAL OR CRITICAL THEORY

How might critical theory or a structural perspective be integrated into the values and ethics of interprofessional collaboration and practice?

Many scholars and policymakers are concerned about the narrow theoretical views that researchers of implicit bias have taken. By focusing on unconscious cognitive structures, social cognition and neuroscientific theories miss the opportunity to also address the role of macro or systemic factors in contributing to health inequities [9; 57]. By focusing on the neurobiology of implicit bias, for example, racism and bias is attributed to central nervous system function, releasing the individual from any control or responsibility. However, the historical legacy of prejudice and bias has roots in economic and structural issues that produce inequities [58]. Larger organizational, institutional, societal, and cultural forces contribute, perpetuate, and reinforce implicit and explicit biases, racism, and discrimination. Psychological and neuroscientific approaches ultimately decontextualize racism [9; 57].

In response to this conflict, a systems-based practice has been proposed [59]. This type of practice emphasizes the role of sociocultural determinants of health outcome and the fact that health inequities stem from larger systemic forces. As a result, medical and health education and training should focus on how patients' health and well-being may reflect structural vulnerabilities driven in large part by social, cultural, economic, and institutional forces. Health and mental health professionals also require social change and advocacy skills to ensure that they can effect change at the organizational and institutional levels [59].

Implicit bias is not a new topic; it has been discussed and studied for decades in the empirical literature. Because implicit bias is a complex and multifaceted phenomenon, it is important to recognize that there may be no one single theory that can fully explain its etiology.

CONSEQUENCES OF IMPLICIT BIASES

HEALTH DISPARITIES

Implicit bias has been linked to a variety of health disparities [1]. Health disparities are differences in health status or disease that systematically and adversely affect less advantaged groups [60]. These inequities are often linked to historical and current unequal distribution of resources due to poverty, structural inequities, insufficient access to health care, and/or environmental barriers and threats [61]. Healthy People 2030 defines a health disparity as [62]:

> …a particular type of health difference that is closely linked with social, economic, and/or environmental disadvantage. Health disparities adversely affect groups of people who have systematically experienced greater obstacles to health based on their racial or ethnic group; religion; socioeconomic status; gender; age; mental health; cognitive, sensory, or physical disability; sexual orientation or gender identity; geographic location; or other characteristics historically linked to discrimination or exclusion.

As noted, in 2003, the Institute of Medicine implicated implicit bias in the development and continued health disparities in the United States [1]. Despite progress made to lessen the gaps among different groups, health disparities continue to exist. One example is racial disparities in life expectancy among Black and White individuals in the United States. Life expectancy for Black men is 4.4 years lower than White men; for Black women, it is 2.9 years lower compared with White women [63]. Hypertension, diabetes, and obesity are more prevalent in non-Hispanic

Black populations compared with non-Hispanic White groups (25%, 49%, and 59% higher, respectively) [64]. In one study, African American and Latina women were more likely to experience cesarean deliveries than their White counterparts, even after controlling for medically necessary procedures [65]. This places African American and Latina women at greater risk of infection and maternal mortality.

Gender health disparities have also been demonstrated. Generally, self-rated physical health (considered one of the best proxies to health) is poorer among women than men. Depression is also more common among women than men [66]. Lesbian and bisexual women report higher rates of depression and are more likely than non-gay women to engage risk behaviors such as smoking and binge drinking, perhaps as a result of LGBTQ+-related stressors. They are also less likely to access healthcare services [67].

Socioeconomic status also affects health care engagement and quality. In a study of patients seeking treatment for thoracic trauma, those without insurance were 1.9 times more likely to die compared with those with private insurance [68].

CLINICAL DECISIONS AND PROVIDER-PATIENT INTERACTIONS

In an ideal situation, health professionals would be explicitly and implicitly objective and clinical decisions would be completely free of bias. However, healthcare providers have implicit (and explicit) biases at a rate comparable to that of the general population [6; 69]. It is possible that these implicit biases shape healthcare professionals' behaviors, communications, and interactions, which may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions [69]. They may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up [7].

In a landmark 2007 study, a total of 287 internal medicine physicians and medical residents were randomized to receive a case vignette of an either Black or White patient with coronary artery disease [70]. All participants were also administered the IAT. When asked about perceived level of cooperativeness of the White or Black patient from the vignette, there were no differences in their explicit statements regarding cooperativeness. Yet, the IAT scores did show differences, with scores showing that physicians and residents had implicit preferences for the White patients. Participants with greater implicit preference for White patients (as reflected by IAT score) were more likely to select thrombolysis to treat the White patient than the Black patient [70]. This led to the possible conclusion that implicit racial bias can influence clinical decisions regarding treatment and may contribute to racial health disparities. However, some argue that using vignettes depicting hypothetical situations does not accurately reflect real-life conditions that require rapid decision-making under stress and uncertainty.

PATIENTS' PERCEPTIONS OF CARE

It has been hypothesized that providers' levels of bias affect the ratings of patient-centered care [34]. Patient-centered care has been defined as patients' positive ratings in the areas of perception of provider concern, provider answering patients' questions, provider integrity, and provider knowledge of the patient. Using data from 134 health providers who completed the IAT, a total of 2,908 diverse racial and ethnic minority patients participated in a telephone survey. Researchers found that for providers who scored high on levels of implicit bias, African American patients' ratings for all dimensions of patient-centered care were low compared with their White patient counterparts. Latinx patient ratings were low regardless of level of implicit bias.

A 2013 study recorded clinical interactions between 112 low-income African American patients and their 14 non-African American physicians for approximately two years [71]. Providers' implicit biases were also assessed using the IAT. In general, the physicians talked more than the patients; however, physicians with higher implicit bias scores also had a higher ratio of physician-to-patient talk time. Patients with higher levels of perceived discrimination had a lower ratio of physician-to-patient talk time (i.e., spoke more than those with lower reported perceived discrimination). A lower ratio of physician-patient talk time correlated to decreased likelihood of adherence.

Another study assessed 40 primary care physicians and 269 patients [72]. The IAT was administered to both groups, and their interactions were recorded and observed for verbal dominance (defined as the time of physician participation relative to patient participation). When physicians scored higher on measures of implicit bias, there was 9% more verbal dominance on the part of the physicians in the visits with Black patients and 11% greater in interactions with White patients. Physicians with higher implicit bias scores and lower verbal dominance also received lower scores on patient ratings on interpersonal care, particularly from Black patients [72].

In focus groups with racially and ethnically diverse patients who sought medical care for themselves or their children in New York City, participants reported perceptions of discrimination in health care [73]. They reported that healthcare professionals often made them feel less than human, with varying amounts of respect and courtesy. Some observed differences in treatment compared with White patients. One Black woman reported [73]:

> When the doctor came in [after a surgery], she proceeded to show me how I had to get up because I'm being released that day "whether I like it or not"… She yanked the first snap on the left leg…So I'm thinking, 'I'm human!' And she was courteous to the White lady [in the next bed], and I've got just as much age as her. I qualify on the level and scale of human being as her, but I didn't feel that from the doctor.

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Another participant was a Latino physician who presented to the emergency department. He described the following [73]:

> They put me sort of in the corner [in the emergency department] and I can't talk very well because I can't breathe so well. The nurse comes over to me and actually says, "Tu tiene tu Medicaid?" I whispered out, "I'm a doctor…and I have insurance." I said it in perfect English. Literally, the color on her face went completely white…Within two minutes there was an orthopedic team around me…I kept wondering about what if I hadn't been a doctor, you know? Pretty eye opening and very sad.

These reports are illustrative of many minority patients' experiences with implicit and explicit racial/ethnic biases. Not surprisingly, these biases adversely affect patients' views of their clinical interactions with providers and ultimately contribute to their mistrust of the healthcare system.

DEVELOPMENTAL MODEL TO RECOGNIZING AND REDUCING IMPLICIT BIAS

There are no easy answers to raising awareness and reducing health providers' implicit bias. Each provider may be in a different developmental stage in terms of awareness, understanding, acceptance, and application of implicit bias to their practice. A developmental model for intercultural sensitivity training has been established to help identify where individuals may be in this developmental journey [74; 75]. It is important to recognize that the process of becoming more self-aware is fluid; reaching one stage does not necessarily mean that it is "conquered" or that there will not be additional work to do in that stage. As a dynamic process, it is possible to move back and forth as stress and uncertainty triggers implicit biases [74]. This developmental model includes six stages:

- Denial: In this stage, the individual has no awareness of the existence of cultural differences between oneself and members of other cultural groups and subgroups. Individuals in this stage have no awareness of implicit bias and cannot distinguish between explicit and implicit biases.
- Defense: In this stage, the person may accept that implicit biases exist but does not acknowledge that implicit biases exist within themselves.
- Minimization: An individual in this stage acknowledges that implicit biases may exist in their colleagues and possibly themselves. However, he or she is uncertain of their consequences and adverse effects. Furthermore, the person believes he or she is able to treat patients in an objective manner.
- Acceptance: In the acceptance stage, the individual recognizes and acknowledges the role of implicit biases and how implicit biases influence interactions with patients.
- Adaptation: Those in the adaptation stage self-reflect and acknowledge that they have unrecognized implicit biases. Not only is there an acknowledgement of the existence of implicit bias, these people begin to actively work to reduce the potential impact of implicit biases on interactions with patients.
- Integration: At this stage, the health professional works to incorporate change in their day-to-day practice in order to mitigate the effects of their implicit biases on various levels—from the patient level to the organization level.

CREATING A SAFE ENVIRONMENT

If psychological safety is threatened, what might be a potential outcome in implicit bias training?

Creating a safe environment is the essential first step to exploring issues related to implicit bias. Discussions of race, stereotypes, privilege, and implicit bias, all of which are very complex, can be volatile or produce heightened emotions. When individuals do not feel their voices are heard and/or valued, negative emotions or a "fight-or-flight" response can be triggered [76]. This may manifest as yelling, demonstrations of anger, or crying or leaving the room or withdrawing and remaining silent [76].

Creating and fostering a sense of psychological safety in the learning environment is crucial. Psychological safety results when individuals feel that their opinions, views, thoughts, and contributions are valued despite tension, conflict, and discomfort. This allows the individual to feel that their identity is intact [76]. When psychological safety is threatened, individuals' energies are primarily expended on coping rather than learning [76]. As such, interventions should not seek to confront individuals or make them feel guilty and/or responsible [77].

When implicit bias interventions or assessments are planned, facilitators should be open, approachable, non-threatening, and knowledgeable; this will help create a safe and inclusive learning environment [77]. The principles of respect, integrity, and confidentiality should be communicated [77]. Facilitators who demonstrate attunement, authenticity, and power-sharing foster positive and productive dialogues about subjects such as race and identity [76]. Attunement is the capacity of an individual to tacitly comprehend the lived experiences of others, using their perspectives to provide an alternative viewpoint for others. Attunement does not involve requiring others to talk about their experiences if they are not emotionally ready [76]. Authenticity involves

being honest and transparent with one's own position in a racialized social structure and sharing one's own experiences, feelings, and views. Being authentic also means being vulnerable [76]. Finally, power-sharing entails redistributing power in the learning environment. The education environment is typically hierarchical, with an expert holding more power than students or participants. Furthermore, other students may hold more power by virtue of being more comfortable speaking/interacting [76]. Ultimately, promoting a safe space lays a foundation for safely and effectively implementing implicit bias awareness and reduction interventions.

STRATEGIES TO PROMOTE AWARENESS OF IMPLICIT BIAS

As discussed, the IAT can be used as a metric to assess professionals' level of implicit bias on a variety of subjects, and this presupposes that implicit bias is a discrete phenomenon that can be measured quantitatively [79]. When providers are aware that implicit biases exist, discussion and education can be implemented to help reduce them and/or their impact.

Another way of facilitating awareness of providers' implicit bias is to ask self-reflective questions about each interaction with patients. Some have suggested using SOAP (subjective, objective, assessment, and plan) notes to assist practitioners in identifying implicit biases in day-to-day interactions with patients [80]. Integrating the following questions into charts and notes can stimulate reflection about implicit bias globally and for each specific patient interaction:

- Did I think about any socioeconomic and/or environmental factors that may contribute to the health and access of this patient?
- How was my communication and interaction with this patient? Did it change from my customary pattern?
- How could my implicit biases influence care for this patient?

When reviewing the SOAP notes, providers can look for recurring themes of stereotypical perceptions, biased communication patterns, and/or types of treatment/interventions proposed and assess whether these themes could be influenced by biases related to race, ethnicity, age, gender, sexuality, or other social characteristics.

A review of empirical studies conducted on the effectiveness of interventions promoting implicit bias awareness found mixed results. At times, after a peer discussion of IAT scores, participants appeared less interested in learning and employing implicit bias reduction interventions. However, other studies have found that receiving feedback along with IAT scores resulted in a reduction in implicit bias [81]. Any feedback, education, and discussions should be structured to minimize participant defensiveness [81].

INTERVENTIONS TO REDUCE IMPLICIT BIASES

Interventions or strategies designed to reduce implicit bias may be further categorized as change-based or control-based [58]. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors [58]. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

PERSPECTIVE TAKING

Perspective taking is a strategy of taking on a first-person perspective of a person in order to control one's automatic response toward individuals with certain social characteristics that might trigger implicit biases [82]. The goal is to increase psychological closeness, empathy, and connection with members of the group [4]. Engaging with media that presents a perspective (e.g., watching documentaries, reading an autobiography) can help promote better understanding of the specific group's lives, experiences, and viewpoints. In one study, participants who adopted the first-person perspectives of African Americans had more positive automatic evaluations of the targeted group [83].

interactive activity

Consuming media that presents a viewpoint and life experience different from your own can help minimize implicit biases. Visit the following sites and consider how they might challenge or expand your perception of each group. Internet searches can help identify many more options for various social groups.

Think Out Loud Podcast
Young Black people share their experiences growing up in Portland, Oregon.
https://podcasts.apple.com/us/podcast/young-black-people-share-their-experiences-growing/id274122573?i=1000496652363

George Takei: Growing Up Asian-American
This PBS clip is a brief introduction, and the subject can be further explored in Takei's book *They Called Us Enemy*.
https://www.pbs.org/wnet/pioneers-of-television/video/george-takei-growing-up-asian-american

Seattle Public Library LGBTQ Staff Picks
A reading list including books and films focusing on LGBTQ+ life, culture, history, and politics.
https://www.spl.org/programs-and-services/social-justice/lgbtq/lgbt-staff-picks

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EMPATHY INTERVENTIONS

Promoting positive emotions such as empathy and compassion can help reduce implicit biases. This can involve strategies like perspective taking and role playing [77]. In a study examining analgesic prescription disparities, nurses were shown photos of White or African American patients exhibiting pain and were asked to recommend how much pain medication was needed; a control group was not shown photos. Those who were shown images of patients in pain displayed no differences in recommended dosage along racial lines; however, those who did not see the images averaged higher recommended dosages for White patients compared with Black patients [84]. This suggests that professionals' level of empathy (enhanced by seeing the patient in pain) affected prescription recommendations.

In a study of healthcare professionals randomly assigned to an empathy-inducing group or a control group, participants were given the IAT to measure implicit bias prior to and following the intervention. Level of implicit bias among participants in the empathy-inducing group decreased significantly compared with their control group counterparts [85].

INDIVIDUATION

Individuation is an implicit bias reduction intervention that involves obtaining specific information about the individual and relying on personal characteristics instead of stereotypes of the group to which he or she belongs [4; 82]. The key is to concentrate on the person's specific experiences, achievements, personality traits, qualifications, and other personal attributes rather than focusing on gender, race, ethnicity, age, ability, and other social attributes, all of which can activate implicit biases. When providers lack relevant information, they are more likely to fill in data with stereotypes, in some cases unconsciously. Time constraints and job stress increase the likelihood of this occurring [69].

MINDFULNESS

Mindfulness requires stopping oneself and deliberately emptying one's mind of distractions or allowing distractions to drift through one's mind unimpeded, focusing only on the moment; judgment and assumptions are set aside. This approach involves regulating one's emotions, responses, and attention to return to the present moment, which can reduce stress and anxiety [86]. There is evidence that mindfulness can help regulate biological and emotional responses and can have a positive effect on attention and habit formation [4]. A mindfulness activity assists individuals to be more aware of their thoughts and sensations. This focus on deliberation moves the practitioner away from a reliance on instincts, which is the foundation of implicit bias-affected practice [4; 87].

Mindfulness approaches include yoga, meditation, and guided imagery. Additional resources to encourage a mindfulness practice are provided later in this course.

Goldstein has developed the STOP technique as a practical approach to engage in mindfulness in any moment [88]. STOP is an acronym for:

- Stop
- Take a breath
- Observe
- Proceed

interactive activity

Visit the following website to view a short animated video on the STOP technique. After viewing the video, consider how you can incorporate the technique into your work.
https://elishagoldstein.com/short-animated-stop-practice-elisha-goldstein-phd

Mindfulness practice has been explored as a technique to reduce activation or triggering of implicit bias, enhance awareness of and ability to control implicit biases that arise, and increase capacity for compassion and empathy toward patients by reducing stress, exhaustion, and compassion fatigue [89]. One study examined the effectiveness of a loving-kindness meditation practice training in improving implicit bias toward African Americans and unhoused persons. One hundred one non-Black adults were randomized to one of three groups: a six-week loving-kindness mindfulness practice, a six-week loving-kindness discussion, or the waitlist control. The IAT was used to measure implicit biases, and the results showed that the loving-kindness meditation practice decreased levels of implicit biases toward both groups [90].

There is also some novel evidence that mindfulness may have neurologic implications. For example, one study showed decreased amygdala activation after a mindfulness meditation [91]. However, additional studies are required in this area before conclusions can be reached.

COUNTER-STEREOTYPICAL IMAGING

Counter-stereotypical imaging approaches involve presenting an image, idea, or construct that is counter to the oversimplified stereotypes typically held regarding members of a specific group. In one study, participants were asked to imagine either a strong woman (the experimental condition) or a gender-neutral event (the control condition) [92]. Researchers found that participants in the experimental condition exhibited lower levels of implicit gender bias. Similarly, exposure to female leaders was found to reduce implicit gender bias [93]. Whether via increased contact with stigmatized groups to contradict prevailing stereotypes or simply exposure to counter-stereotypical imaging, it is possible to unlearn associations underlying various implicit biases. If the social environment is important in priming positive evaluations, having more

positive visual images of members in stigmatized groups can help reduce implicit biases [94]. Some have suggested that even just hanging photos and having computer screensavers reflecting positive images of various social groups could help to reduce negative associations [94].

EFFECTIVENESS OF IMPLICIT BIAS INTERVENTIONS

The effectiveness of implicit bias trainings and interventions has been scrutinized. In a 2019 systematic review, different types of implicit bias reduction interventions were evaluated. A meta-analysis of empirical studies published between May 2005 and April 2015 identified eight different classifications of interventions [13]:

- Engaging with others' perspectives, consciousness-raising, or imagining contact with outgroup: Participants either imagine how the outgroup thinks and feels, imagine having contact with the outgroup, or are made aware of the way the outgroup is marginalized or given new information about the outgroup.
- Identifying the self with the outgroup:Participants perform tasks that lessen barriers between themselves and the outgroup.
- Exposure to counter-stereotypical exemplars: Participants are exposed to exemplars that contradict negative stereotypes of the outgroup.
- Appeal to egalitarian values: Participants are encouraged to activate egalitarian goals or think about multiculturalism, cooperation, or tolerance.
- Evaluative conditioning: Participants perform tasks to strengthen counter-stereotypical associations.
- Inducing emotion: Emotions or moods are induced in participants.
- Intentional strategies to overcome biases: Participants are instructed to implement strategies to over-ride or suppress their biases.
- Pharmacotherapy

Interventions found to be the most effective were, in order from most to least, [13]:

- Intentional strategies to overcome biases
- Exposure to counter-stereotypical exemplars
- Identifying self with the outgroup
- Evaluative conditioning
- Inducing emotions

In general, the sample sizes were small. It is also unclear how generalizable the findings are, given many of the research participants were college psychology students. The 30 studies included in the meta-analysis were cross-sectional (not longitudinal) and only measured short-term outcomes, and there is some concern about "one shot" interventions, given the fact that implicit biases are deeply embedded. Would simply acknowledging the existence of implicit biases be sufficient to eliminate them [95; 96]? Or would such a confession act as an illusion to having self-actualized and moved beyond the bias [95]?

Optimally, implicit bias interventions involve continual practice to address deeply habitual implicit biases or interventions that target structural factors [95; 96].

ROLE OF INTERPROFESSIONAL COLLABORATION AND PRACTICE AND IMPLICIT BIASES

The study of implicit bias is appropriately interdisciplinary, representing social psychology, medicine, health psychology, neuroscience, counseling, mental health, gerontology, LGBTQ+ studies, religious studies, and disability studies [13]. Therefore, implicit bias empirical research and curricula training development lends itself well to interprofessional collaboration and practice (ICP).

One of the core features of IPC is sharing—professionals from different disciplines share their philosophies, values, perspectives, data, and strategies for planning of interventions [97]. IPC also involves the sharing of roles, responsibilities, decision making, and power [98]. Everyone on the team employs their expertise, knowledge, and skills, working collectively on a shared, patient-centered goal or outcome [98; 99].

Another feature of IPC is interdependency. Instead of working in an autonomous manner, each team member's contributions are valued and maximized, which ultimately leads to synergy [97]. At the heart of this are two other key features: mutual trust/respect and communication [99]. In order to share responsibilities, the differing roles and expertise are respected.

Experts have recommended that a structural or critical theoretical perspective be integrated into core competencies in healthcare education to teach students about implicit bias, racism, and health disparities [100]. This includes [100]:

- Values/ethics: The ethical duty for health professionals to partner and collaborate to advocate for the elimination of policies that promote the perpetuation of implicit bias, racism, and health disparities among marginalized populations.
- Roles/responsibilities: One of the primary roles and responsibilities of health professionals is to analyze how institutional and organizational factors promote racism and implicit bias and how these factors contribute to health disparities. This analysis should extend to include one's own position in this structure.
- Interprofessional communication: Ongoing discussions of implicit bias, perspective taking, and counter-stereotypical dialogues should be woven into day-to-day practice with colleagues from diverse disciplines.

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- Teams/teamwork: Health professionals should develop meaningful contacts with marginalized communities in order to better understand whom they are serving.

Adopting approaches from the fields of education, gender studies, sociology, psychology, and race/ethnic studies can help build curricula that represent a variety of disciplines [78]. Students can learn about and discuss implicit bias and its impact, not simply from a health outcomes perspective but holistically. Skills in problem-solving, communication, leadership, and teamwork should be included, so students can effect positive social change [78].

CONCLUSION

In the more than three decades since the introduction of the IAT, the implicit bias knowledge base has grown significantly. It is clear that most people in the general population hold implicit biases, and health professionals are no different. While there continue to be controversies regarding the nature, dynamics, and etiology of implicit biases, it should not be ignored as a contributor to health disparities, patient dissatisfaction, and suboptimal care. Given the complex and multifaceted nature of this phenomenon, the solutions to raise individuals' awareness and reduce implicit bias are diverse and evolving.

RESOURCES

American Bar Association
Diversity and Inclusion Center
Toolkits and Projects
https://www.americanbar.org/groups/diversity/resources/toolkits

National Implicit Bias Network
https://implicitbias.net/resources/resources-by-category

The Ohio State University
The Women's Place: Implicit Bias Resources
https://womensplace.osu.edu/resources/implicit-bias-resources

The Ohio State University
Kirwan Institute for the
Study of Race and Ethnicity
http://kirwaninstitute.osu.edu

University of California, Los Angeles
Equity, Diversity, and Inclusion: Implicit Bias
https://equity.ucla.edu/know/implicit-bias

University of California, San Francisco,
Office of Diversity and Outreach
Unconscious Bias Resources
https://diversity.ucsf.edu/resources/unconscious-bias-resources

Unconscious Bias Project
https://unconsciousbiasproject.org

MINDFULNESS RESOURCES

University of California, San Diego
Center for Mindfulness
https://medschool.ucsd.edu/som/fmph/research/mindfulness

University of California, Los Angeles
Guided Meditations
https://www.uclahealth.org/marc/mindful-meditations

Mindful: Mindfulness for Healthcare Professionals
https://www.mindful.org/mindfulhome-mindfulness-for-healthcare-workers-during-covid

FACULTY BIOGRAPHY

Alice Yick Flanagan, PhD, MSW, received her Master's in Social Work from Columbia University, School of Social Work. She has clinical experience in mental health in correctional settings, psychiatric hospitals, and community health centers. In 1997, she received her PhD from UCLA, School of Public Policy and Social Research. Dr. Yick Flanagan completed a year-long post-doctoral fellowship at Hunter College, School of Social Work in 1999. In that year she taught the course Research Methods and Violence Against Women to Masters degree students, as well as conducting qualitative research studies on death and dying in Chinese American families.

Previously acting as a faculty member at Capella University and Northcentral University, Dr. Yick Flanagan is currently a contributing faculty member at Walden University, School of Social Work, and a dissertation chair at Grand Canyon University, College of Doctoral Studies, working with Industrial Organizational Psychology doctoral students. She also serves as a consultant/subject matter expert for the New York City Board of Education and publishing companies for online curriculum development, developing practice MCAT questions in the area of psychology and sociology. Her research focus is on the area of culture and mental health in ethnic minority communities.

Customer Information/Evaluation insert located between pages 48–49.

Psychopharmacology

Includes 10 Pharmacotherapeutic/Pharmacology Hours

Audience
This course is designed for nurses and pharmacy professionals involved in the care of patients with mental health conditions.

Course Objective
The purpose of this course is to provide members of the interprofessional healthcare team with the information necessary to appropriately prescribe, administer, and dispense psychopharmacotherapy, with the ultimate goal of improving patient care and public health.

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

1. Outline the history of pharmacology in psychiatry.
2. Describe the action and use of typical antipsychotics.
3. Compare and contrast the various atypical antipsychotics.
4. Evaluate class-wide adverse effects of antipsychotics.
5. Identify available antidepressant medication and their use in the treatment of major depression.
6. Discuss potential adverse effects and warnings associated with antidepressants.
7. Describe medications used in the management of bipolar disorder.
8. Assess the role of antidepressants in the management of anxiety disorders.
9. Discuss the use of benzodiazepines for the treatment of anxiety.
10. Review available pharmacotherapy to incorporate into the treatment of substance use disorders.

Faculty
Carol Whelan, APRN, has been working in nursing education since 2000. She received her Master's degree in psychiatric/mental health nursing from St. Joseph College in West Hartford, Connecticut, and completed post-graduate nurse practitioner training at Yale University. Ms. Whelan is an Associate Clinical Professor and Lecturer at Yale University and works as an APRN at the Department of Veterans' Affairs in Connecticut, where she also serves as the Vice President of Medical Staff. She has authored many articles, textbook chapters, and books.

Faculty Disclosure
Contributing faculty, Carol Whelan, APRN, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Division Planner
Jane C. Norman, RN, MSN, CNE, PhD

Division Planner Disclosure
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INTRODUCTION

Psychiatry and the medications prescribed for psychiatric issues are so intertwined with culture and society that it is impossible to discuss its history without also talking about the societal context and cultural beliefs that surround it. No orthopedic surgeon has ever had to convince a patient that a broken leg was not caused by demons and that the therapy prescribed is medically needed. The same cannot be said for psychiatry. Even in the 21st century, clinicians who deal with the complex medications used to treat psychiatric illness encounter patients who feel shame, guilt, and doubt associated with their diagnoses and the medications used to manage them.

The root of this skepticism can be traced to the French philosopher René Descartes in the 1500s and the famous Cartesian motto "I think therefore I am." According to this widely embraced philosophy, one exists because s/he thinks, not because the heart beats, the muscles work, or the lungs breathe. From this perspective, one is because their brain is healthy.

Given this belief that a disordered mental state calls one's very existence into question, it is no wonder patients are reluctant to seek help, ashamed to report their symptoms, and afraid that they may lose their job or custody of their children—there is an underlying belief that their existence will be questioned if something is wrong with their thoughts, emotions, and the inner core of their being. This is the world in which psychiatric medications are being prescribed. But how did we get here?

A BRIEF HISTORY OF PSYCHIATRY AND PSYCHOPHARMACOLOGY

In the United States, the first attempt at humane treatment of psychiatric disorders was by the Quakers, who, in 1752, used the Pennsylvania Hospital in Philadelphia to house patients in its basement; however, the environment in the hospital was damaging to patients, some of whom were shackled to walls [1]. Other early institutions for people deemed "mentally disturbed" were opened in the late 1700s in New York. In 1824, the Eastern Lunatic Asylum (now Eastern State Hospital) opened in Lexington, Kentucky. By 1890, every state had at least one publicly supported mental hospital, with populations that were rapidly expanding; by the 1950s, these institutions housed more than 500,000 patients [1]. One of the earliest practitioners of what could be called psychiatry was Dr. Benjamin Rush, who has been called the father of American psychiatry and who wrote the first American textbook on mental diseases (*Medical Inquiries and Observations upon Diseases of the Mind*) in 1812.

EARLY CUSTODIAL CARE AND THE ADVENT OF INSTITUTIONS

The Association of Medical Superintendents of American Institutions for the Insane was founded in 1844; in 1921, the name changed to the American Psychiatric Association (APA) [2]. In the 1800s, there was no real psychopharmacology or even a true appreciation of the biologic nature of mental illness. However, it is important to acknowledge Rush's decision to refer to "diseases of the mind," rather than more judgmental terminology common to the time, such as spiritual disease or weakness. In fact, Rush hypothesized that psychiatric disorders were caused by irritation of the blood vessels in the brain. This led to treatments such as bleeding and purging and to what could be called the first attempt at the development of a psychoactive medication—the use of mercury as a treatment for mental illness. While it is easy to dismiss such early attempts, this theory of a vascular cause of psychiatric symptoms is consistent with some current knowledge of vascular dementia, and while the theories seem ill-informed today, it is important to note that other popular theories of psychiatric etiology of the time attributed mental illness to demons, witchcraft, or moral turpitude.

During this early period, institutional care of the mentally ill was often a means to persecute women and others whom society wished to confine, which led to what some call the "coercive era" of psychiatric care. One of the most important of these cases was that of Elizabeth Packard in 1860. Elizabeth Packard was married to a clergyman who forcibly placed her in an Illinois asylum. In 1860, Illinois law allowed for involuntary hospitalization of a spouse (generally a wife) by request without any evidence. Ms. Packard was eventually able to obtain release from the hospital, but due to her husband's continuing campaign, she was forced to petition the court and was released in 1863 with a habeas corpus hearing. After gaining her freedom, Ms. Packard began a campaign for the protection of women's rights. As a result of her efforts and the efforts of others at the time, laws were passed requiring a jury trial prior to involuntary hospitalization. It is notable that the Association of Medical Superintendents of American Institutions for the Insane (now the APA) opposed these laws at the time. The damage done by these forcible hospitalizations was huge, and the association of psychiatry with coercion persists to this day. These beliefs influence both the public's acceptance of psychopharmacology as a valid and effective treatment and the acceptance of psychiatric diagnoses as true medical diagnoses, as opposed to an excuse to prescribe medications or force hospitalization.

Another leader in the development of humane custodial care of the psychiatric patients was Dorothea Dix, who, in addition to her other accomplishments, is credited with opening more than 30 state mental hospitals throughout the United States. Dix advocated for humane institutions, particularly for the poor and unhoused, and reformation of mental health treatment.

The landmark court case O'Connor v. Donaldson ruled that the government cannot confine an individual who is not dangerous and is capable of living outside the institution. This ruling was based on the case of Kenneth Donaldson, who in his youth had undergone a course of brief psychiatric care, but had recovered, married, and moved from Florida to Pennsylvania. In 1956, he travelled to Florida to visit his parents, where he made a remark (possibly a joke) that he believed someone in Pennsylvania may have been trying to poison his food. In response, his father hired a lawyer, and at a hearing (where he had no legal representation), Donaldson was civilly committed. He was then placed in a housing unit with dangerous and violent criminals. He received no treatment and, as a Christian Scientist, refused all medications and did not agree that he was experiencing mental illness, which was against the typical routine of admitting illness, accepting treatment, and being released. Donaldson spent more than 15 years in this asylum, despite friends petitioning the administrator for his release and guaranteeing that they would care for him. He eventually won his release by petitioning the courts directly and then proceeded to file suit against the administrator (O'Connor) who had blocked his release, on the constitutional ground of illegal confinement denying him his right to liberty.

The court found that mental illness alone cannot justify custodial confinement against the will of the individual. Further cases (e.g., Lake v. Cameron) introduced the concept of care in the least restrictive setting, and in 1999, the Supreme Court ruled in Olmstead v. L.C. that mental illness is a disability covered under the Americans with Disabilities Act.

At the same time that the courts were acknowledging the rights of persons with mental illness, pharmacologists were making breakthroughs; therapeutic use of chlorpromazine (Thorazine) had been discovered, and the world of psychiatry would never be the same.

THE BIRTH OF MODERN PSYCHIATRY AND PSYCHOPHARMACOLOGY

The history of psychopharmacology is intertwined with the history of neurology and psychiatry. During the 19th century, psychiatry and neurology were chiefly concerned with the treatment of psychosis and deviant behaviors. The treatment of less severe conditions (e.g., depression, neurosis) was considered outside the province of psychiatry or neurology.

At the beginning of the 20th century, Sigmund Freud published his famous theories on the unconscious roots of what he termed psychoneurosis [3]. He was especially interested in conversion disorders, whereby patients displayed paralysis or other somatic symptoms that could not be explained in a medical context. Freud developed psychoanalysis (talk therapy) and thus began the outpatient treatment of patients with psychiatric concerns.

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By the mid-20th century, psychoanalysis became overwhelmingly popular and was employed not only in the treatment of patients with anxiety or neurosis but also in the treatment of patients with more severe psychiatric disorders, such as psychosis, for which talk therapy had little to offer. Some postulate that the development of psychoanalysis stunted the development of psychopharmacology by promoting the notion that talk therapy could effectively treat all mental health issues.

One of the first treatments of psychosis—electroconvulsive therapy or ECT—was developed in the 1930s. Its development arose from the observation that patients with both psychosis and epilepsy seemed to experience improvements in psychotic symptoms following a seizure. While this apparent improvement may have actually been a postictal phase of the seizure disorder, it spurred a search for ways to induce seizures in patients with severe psychiatric disorders. Initial attempts used high doses of stimulant drugs to produce seizures, and the term convulsive therapy was coined. Due to drawbacks evident with the use of stimulant drugs, Italian neurologist Ugo Cerletti experimented with inducing seizures using electrical shocks delivered to the head [4].

Despite its roots in somewhat dubious observations of the effects of electric shocks on livestock, ECT remains in use today as a valid psychiatric treatment. In fact, it was one of the only truly effective psychiatric treatments in the 1930s and 1940s. It was also arguably one of the first treatments to address mental illness as a biologic disorder. Some consider the advent of convulsive therapy as the true beginning of psychopharmacology, as it relied on alteration of brain chemistry to produce improvements in patients.

Building on these advances, psychopharmacology exploded in the 1950s with the development of chlorpromazine, early antidepressants, and early mood stabilizers.

THE DEVELOPMENT OF PSYCHOPHARMACOLOGY

Most experts date the birth of modern psychopharmacology to the synthesis of which drug?

The term psychopharmacology traces its roots to 1920, appearing first in the title of a paper by David Macht describing the use of quinine and antipyretics in tests on neuromuscular coordination. However, most experts date the true birth of psychopharmacology to 1951, when chlorpromazine was first synthesized [5].

Chlorpromazine was developed in the lab of Rhône-Poulenc (an early French pharmaceutical company) for use in general anesthesia to induce calmness. It was not long before French surgeons saw the potential for the use of chlorpromazine in the treatment of psychiatric illness. The first paper on chlorpromazine (titled "A new stabilizer") was published in February 1952 in La Presse Medicale [5].

The first documented clinical psychiatric use of chlorpromazine was on January 19, 1952, when 50 mg intravenous (IV) chlorpromazine was given to a patient, 24 years of age, with severe agitation, psychosis, and possibly mania. The effects were noted as calming but also were transient in nature. After 20 days of treatment with a cumulative total of 900 mg of chlorpromazine along with concomitant barbiturates and ECT, the patient was able to be discharged home [5]. By 1957, chlorpromazine had become internationally recognized, and the American Public Health Association presented Albert Lasker Awards for Medical Research to several scientists and physicians associated with the development of chlorpromazine and introduction of the drug into clinical practice.

Perhaps the greatest contribution of chlorpromazine was not in its clinical effects but rather in its ability to distinguish the biologic basis of schizophrenia. During the course of the 1950s, studies of chlorpromazine use led to an understanding of synaptic transmission and development of the theory that synaptic transmission was not a merely electrical event but rather a chemically mediated event. By the end of the 1950s, six neurotransmitters had been identified in the central nervous system, including dopamine, norepinephrine, and serotonin [5].

The success of chlorpromazine led to the development of more antipsychotics, including thioridazine (Mellaril), haloperidol (Haldol, decanoate), trifluoperazine (Stelazine), and fluphenazine (Prolixin). However, all of these early antipsychotics were noted to have neurologic side effects, most notably extrapyramidal symptoms with parkinsonian features.

Some consider the 1950s to be a "golden age" of psychopharmacology. Beginning in 1958, tricyclic compounds based on the structure of imipramine were synthesized; these are referred to as second-generation (atypical) antipsychotics. One of these compounds was clozapine (Clozaril, Versacloz), an antipsychotic still in use today. Interestingly, clozapine did not initially attract much attention. Small trials showed mixed results, and unlike chlorpromazine, there was no consensus as to its effectiveness. The lack of extrapyramidal side effects led many researchers to erroneously believe that it was not a true antipsychotic, as the dopamine blockade theory of schizophrenia was still widely held.

THE ORGANIC BASIS OF MENTAL ILLNESS AND THE ADVANCEMENT OF PSYCHOPHARMACOLOGY

The development of medications to treat psychiatric illnesses has greatly informed our understanding of the biologic nature of these illnesses—most notably the link between antipsychotics and schizophrenia. This translational research also led to the understanding of neurotransmitters and further informed the development of large classes of psychoactive medications.

The dopamine receptor D2 is a common target of the antipsychotics. Assessment of medications' ability to target receptors was made possible by the introduction of the spectrophotofluorimeter in 1955. This instrument allows for analysis of chemicals in the brain, including monoamines, which allowed for the further advancement of the field of psychopharmacology [5].

With their introduction in the 1950s, monoamine oxidase inhibitors (MAOIs) became the first class of medications used to treat depression. The incorporation of these agents into clinical practice further moved psychiatry away from inpatient care in institutions toward effective outpatient care.

Another historical breakthrough in psychopharmacology was the discovery of the use of lithium for the treatment of mania. While there is some evidence of usage in the 1800s, the seminal research reintroducing lithium for the treatment of mania was published in 1949 by John Cade [6]. Despite its ready availability and widespread use worldwide, lithium was not approved by the U.S. Food and Drug Administration (FDA) until 1970; the United States was the 50th country to approve the use of lithium for the management of mania [6].

The discovery of medications effective in the treatment of affective disorders induced a shift away from the talk therapy-only approach originally developed by Freud. Further, the ability of lithium to improve symptoms of depression supported the burgeoning biologic theory of mental illness. This change in understanding of mental illness had extensive and widespread influence on the practice of psychiatry. It extended beyond schizophrenia and bipolar disorder and helped transform etiologic theories of diseases such as autism from a focus on environmental influence (e.g., poor mothering in the case of autism) to a biologic understanding of psychiatric disorders prevalent today.

In the later part of the 20th century, psychopharmaceutical advancements continued at record pace. The development of benzodiazepines, lithium, barbiturates, and MAOIs led to an era of deinstitutionalization and the mainstream diagnosis and management of psychiatric disorders without a reliance on talk therapy. This seismic change was not without controversy, and proponents of talk therapy and psychoanalysis resisted the use of psychopharmacology to treat mental illness.

This philosophical conflict was clearly evident in the revision process for the APA's *Diagnostic and Statistical Manual of Mental Disorders* (DSM). In 1980, the DSM was extensively revised (creating the DSM-III), and psychoanalytic language was abandoned. In contrast to the DSM-II, the DSM-III focused on symptom-based descriptions of mental disorders for diagnostic criteria.

Psychiatry continued to evolve to accept the biologic basis of mental illness and embrace the use of pharmacologic treatment. The introduction of selective serotonin reuptake inhibitors (SSRIs), which were both well-tolerated and had better safety profiles than previous medications, revolutionized the treatment of depression. The first SSRI, fluoxetine (Prozac), was approved by the FDA in 1987. While there has been controversy regarding the possible overdiagnosing of depression or overprescribing of antidepressants, no one disputes the enormous impact fluoxetine has had on psychopharmacology [3].

At virtually the same time as the introduction of fluoxetine, a group of second-generation (atypical) antipsychotics were being approved in the United States. These medications, including risperidone (Perseris, Risperdal) and olanzapine (Zyprexa), challenged the traditional belief that only the D2 receptor/dopamine was involved in psychosis. This renewed interest in the forgotten medication clozapine and novel treatment approaches for schizophrenia.

While clozapine had been originally introduced in the 1950s and approved by the FDA in 1971, small studies had been unable to show efficacy. Use of the drug effectively ended in 1975, when the Finnish National Board of Health reported 18 individuals prescribed clozapine who developed severe blood disorders (most commonly agranulocytosis, a severe decrease or an absence of white blood cells increasing the risk of potentially fatal infection); 9 of these patients died [7]. Research since that time indicates that agranulocytosis occurs in about 1% of patients taking clozapine and neutropenia is seen in about 3% [8].

These early roadblocks to the use of clozapine were overcome, first by a system of monitoring white blood cell counts and secondly by longer studies that showed that the effects of clozapine continue to increase after four weeks of therapy, unlike chlorpromazine, which had a peak effect after two to three weeks [7]. As a result of these findings, clozapine was approved for the treatment of psychosis in the United States in 1990 [7]. The price of this drug when it was first approved, approximately $9,000 per patient per year for the medication and monitoring, was initially controversial, but it was more cost-effective than inpatient care or institutionalization [3; 7].

The risk for leukopenia remains a barrier to wider use of clozapine; however, it has become a mainstay for treatment-resistant schizophrenia and is also acknowledged to reduce the risk of suicide in patients with schizophrenia. It is also used off-label in the management of treatment-resistant bipolar disorder and dementia- or Parkinson-related psychosis or agitation. With the availability of a generic version, the price of clozapine is now less than many other newer antipsychotics. Knowledge that the risk of agranulocytosis is highest in the first three months has also led to a reduction in the frequency of long-term monitoring.

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NEW HORIZONS: PSYCHOPHARMACOLOGY AND ADDICTION MEDICINE

Substance use disorder is a significant issue in the United States, affecting more than 20 million individuals annually [9]. Historically, addiction was considered a moral failing—a symptom of criminality or weak character. A variety of non-effective treatments were used until the 1900s, ranging from cocaine-based therapy, hydrotherapy, and institutionalization. In the 1930s, 12-step and self-help models were established for alcohol dependence treatment. In 1949, disulfiram (Antabuse) became the first drug approved to treat alcoholism [10]. The drug works by increasing the concentration of acetaldehyde, a toxic byproduct that occurs when alcohol is broken down in the body. Excess amounts of this byproduct (as when alcohol is consumed along with the medication) cause unpleasant symptoms, such as nausea and flushing of the skin. The anticipation of these effects can assist with cessation and abstinence. For more than 40 years, disulfiram was the only medication approved for the treatment of alcohol use disorder [10]. Since then, two additional medications—naltrexone (ReVia, Vivitrol) and acamprosate (Campral)—have been approved. The conceptualization of addiction and substance use disorder has also evolved and is now recognized to be a primary, chronic disease of brain reward, motivation, memory, and related circuitry. Dysfunction in these circuits leads to characteristic biologic, psychological, social, and spiritual manifestations [11]. As a primarily biologic illness, addiction is now recognized as a valid target for pharmacotherapy.

In the early 21st century, the United States experienced an unprecedented increase in opioid prescribing, use disorder, and fatal overdose [12]. In addition to the highly beneficial therapeutic effects, the toxic side effects and addictive potential of opioids have been known for centuries. These undesired effects have prompted a search for a potent synthetic opioid analgesic free of addictive potential and other complications. However, all synthetic opioids introduced into medical use share the same abuse liabilities of the classical opioids. The search for new opioid therapeutics has resulted in the synthesis of opioid antagonists and compounds with mixed agonist-antagonist properties, such as buprenorphine, which has expanded therapeutic options and provided the basis of expanded knowledge of opioid mechanisms [13].

Nonmedical use of prescription opioids was reported in literature as early as 1880. A report in 1928 documented that injection of opioids contributed to the development of nonmedical use and misuses of prescription opioids. Before 1930, the prevalence of nonmedical opioid injecting in the United States was low. But by the mid-1940s, more than one-half the admissions to the National Institute of Mental Health's Lexington Hospital were for the misuse of prescription opioids [14]. As of 2018, there were an estimated 2.1 million individuals with opioid use disorder in the United States [15]. In addition, more than 81,000 drug overdose deaths occurred in the United States in the 12 months ending in May 2020, the highest number of overdose deaths ever recorded in a 12-month period, and the rise was mainly attributed to synthetic opioids [16].

While methadone has long been in use in specialized clinics with strict licensing, the development of alternative treatments for opioid use disorder, including buprenorphine/naloxone (Suboxone), has revolutionized the approach to managing and treating this disorder.

ANTIPSYCHOTIC MEDICATIONS

With the development of clozapine, antipsychotic medications have been divided into typical antipsychotics (also referred to as first-generation antipsychotics) and atypical antipsychotics (also referred to as second-generation antipsychotics). In addition, a group of novel atypical antipsychotics have been developed and generally act on serotonin as well as dopamine receptors.

The choice of antipsychotic should be guided by the side effect profile, available route of administration (e.g., liquid forms, oral disintegrating tablets), and the patient's medical history, current medications, and preference. Many patients will be unwilling to switch from a drug that has been effective, even if a different drug may yield better results.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Psychiatric Association recommends that patients with schizophrenia be treated with an antipsychotic medication and monitored for effectiveness and side effects. This guideline statement should be implemented in the context of a person-centered treatment plan that includes evidence-based nonpharmacological and pharmacological treatments for schizophrenia.

(https://psychiatryonline.org/doi/full/10.1176/appi.books.9780890424841.Schizophrenia02. Last accessed September 28, 2021.)

Strength of Recommendation/Level of Evidence: IA (High confidence that the evidence reflects the true effect)

TYPICAL ANTIPSYCHOTICS

Which typical antipsychotic may be administered via inhalation?

Typical antipsychotics (***Table 1***) have a primary site of action at the D2 receptor and are potent D2 receptor blockers. They also have noradrenergic, cholinergic, and histaminergic blocking action. These agents can also be described as high,

TYPICAL ANTIPSYCHOTIC MEDICATIONS					
Drug	**Dose Range**	**Typical Starting Dose**	**Usual Maintenance Dose[a]**	**Route(s)**	**Indication(s)**
Chlorpromazine	25–800 mg/day	25–50 mg/day	100–400 mg daily or BID	IM, IV, PO	Schizophrenia, bipolar disorder, intractable hiccups, agitation/aggression (severe, acute) associated with psychiatric disorders
Droperidol	0.625–10 mg/day	2.5–10 mg/day	10 mg/day	IM, IV	Postoperative nausea/vomiting, acute undifferentiated agitation (off-label)
Flupentixol	IM: 5–40 mg/day Oral: 1–6 mg/day	IM: 5–20 mg/day Oral: 1 mg/day	IM: 20–40 mg every 2 to 3 weeks Oral: 3–6 mg/day in divided doses	Oral, IM (depot)	Schizophrenia
Fluphenazine	2.5–40 mg/day	2.5–10 mg every 6 to 8 hours	Oral: 5–40 mg/day IM: 12.5–25 mg every 2 to 4 weeks	PO, IM, decanoate	Psychotic disorders
Haloperidol (Haldol)	0.5–30 mg/day	Oral: 0.5–5 mg BID	5–15 mg BID	PO, IM, IV, decanoate	Bipolar disorder, hyperactive delirium, schizophrenia, Tourette-associated tics, acute/severe agitation (off-label)
Loxapine (Adasuve)	5–125 mg BID	10–25 mg BID	60–100 mg BID	PO, inhalation	Schizophrenia, acute agitation
Methotrimeprazine	6–200 mg/day	Mild: 6–25 mg/day in divided doses Severe: 50–75 mg/day in divided doses	Oral: IM: 75–100 mg/day in divided doses	PO, IM	Anxiety/tension disorders, insomnia, nausea/vomiting, pain, psychotic disorders
Molindone	5–75 mg TID	5–15 mg BID	10–25 mg TID	PO	Schizophrenia
Periciazine	5–40 mg/day	5–20 mg in the morning, followed by 10–40 mg in the evening	Titrate to lowest effective dose	PO	Psychosis
Perphenazine	2–24 mg BID	2–4 mg BID	8–24 mg BID	PO	Schizophrenia, nausea/vomiting
Pimozide	0.5–10 mg/day	1–2 mg/day in divided doses	Lowest effective dose (maximum: 10 mg)	PO	Tourette syndrome, delusional infestation (off-label)

Table 1 continues on next page.

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TYPICAL ANTIPSYCHOTIC MEDICATIONS *(Continued)*					
Drug	**Dose Range**	**Typical Starting Dose**	**Usual Maintenance Dose[a]**	**Route(s)**	**Indication(s)**
Prochlorperazine (Compro)	2.5–25 mg/day	Oral: 5–10 mg every 6 to 8 hours IM: 5–10 mg every 3 to 4 hours IV: 2.5–10 mg every 3 to 4 hours Rectal: 25 mg every 12 hours	Maximum: 40 mg/day	PO, IM, IV, rectal	Acute nausea and vomiting
Thioridazine	50–800 mg/day	50–100 mg TID	200–800 mg BID or QID	PO	Schizophrenia
Thiothixene	2–30 mg BID	2–5 mg BID	10–15 mg BID	PO	Schizophrenia
Trifluoperazine	2–40 mg/day	1–2mg BID	15–20 mg/day	PO	Schizophrenia
Zuclopenthixol	10–400 mg/day	Oral: 10–50 mg/day in divided doses IM: 50–150 mg/day	Oral: 20–40 mg/day IM: Up to a maximum 400 mg/day	PO, IM	Schizophrenia, psychoses (acute and long-term)

[a]All dosing is for adults. For pediatric uses, consult pediatric-specific literature.
BID = twice daily, IM = intramuscular, IV = intravenous, PO = oral, QID = four times per day, TID = three times per day.

Source: [17; 18; 19] *Table 1*

intermediate, or low potency. High-potency antipsychotics are prescribed in lower doses, with the most widely prescribed of these being haloperidol (Haldol). Haloperidol is available in oral, intramuscular (IM), and long-acting IM decanoate formulations. Low-potency antipsychotics are prescribed in higher doses; the most widely used of these is chlorpromazine [17; 18].

Adverse Effects

The adverse and side effect profiles of typical antipsychotics are generally poorer than the atypical antipsychotics. The prevention, detection, and treatment of extrapyramidal symptoms, most notably tardive dyskinesia, is the main challenge when prescribing typical antipsychotics.

Neurologic Effects

Patients who are prescribed typical antipsychotics should be monitored for neurologic side effects using the standardized Abnormal Involuntary Movement Scale (AIMS) (***Figure 1***).

The AIMS consists of 12 items and can usually be completed within 10 minutes. It was developed specifically to detect and record the occurrence of tardive dyskinesia in any patient taking neuroleptic medication. Tardive dyskinesia is a syndrome characterized by abnormal involuntary movements of the patient's face, mouth, trunk, or limbs, and it affects 20% to 30% of patients who have been treated for months or years with neuroleptic medications. Patients who are older, are heavy smokers, or have diabetes are at increased risk of developing tardive dyskinesia. For most patients, this side effect develops three months after the initiation of neuroleptic therapy; in elderly patients, however, tardive dyskinesia can develop after as little as one month [20].

Regular use of the AIMS allows the severity of symptoms to be followed over time. Initial AIMS testing should be done prior to the initiation of treatment and every three to six months during therapy. Either before or after completing the examination procedure, the patient should be observed

ABNORMAL INVOLUNTARY MOVEMENT SCALE (AIMS)

Patient Name _____ Date of Visit _____

Code: 0 = None 1 = Minimal 2 = Mild 3 = Moderate 4 = Severe

Movement Ratings:
- Rate highest severity observed in category I, II, III.
- Rate movements that occur upon activation one point less than those observed spontaneously.
- Circle movements as well as code number that applies.

		RATER / DATE	RATER / DATE	RATER / DATE	RATER / DATE
I FACIAL & ORAL MOVEMENTS	**1. Muscles of Facial Expression** e.g. movements of forehead, eyebrows, periorbital area, cheeks, including frowning, blinking, smiling, grimacing	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	2. Lips and Perioral Area e.g. puckering, pouting, smacking	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	3. Jaw Biting, clenching, chewing, mouth opening , lateral movement	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	4. Tongue Rate only increases in movement both in and out of mouth. NOT inability to sustain movement. Darting in and out of mouth	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
II EXTREMITY MOVEMENTS	**5. Upper (arms, wrists, hands, fingers)** Include choreic movements (i.e. rapid objectively purposeless, irregular, spontaneous) athetoid movements. DO NOT INCLUDE TREMOR (i.e. repetitive, regular, rhythmic)	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	6. Lower (legs, knees, ankles, toes) Lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
III TRUNK MOVEMENTS	**7. Neck, shoulders and hips** Rocking, twisting, squirming, pelvic gyrations	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
IV GLOBAL JUDGEMENT	**8. Severity of abnormal movements overall**	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	9. Incapacitation due to abnormal movements	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	10. Patient's awareness of abnormal movements. Rate only patients report: No Awareness = 0 Aware, no distress = 1 Aware, mild distress = 2 Aware, moderate distress = 3 Aware, severe distress = 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
V DENTAL STATUS	**11. Current problems with teeth and/or dentures**	YES NO	YES NO	YES NO	YES NO
	12. Are dentures usually worn	YES NO	YES NO	YES NO	YES NO
	13. Endentia?	YES NO	YES NO	YES NO	YES NO
	14. Do movements disappear with sleep?	YES NO	YES NO	YES NO	YES NO

Source: [20] *Figure 1*

unobtrusively at rest (e.g., in the waiting area). The chair used in the examination should be firm and without arms. The patient should remove his or her shoes and socks and any gum, candy, or food from his/her mouth prior to the examination. In addition to the examination and observation, the patient should be asked about:

- Dental/oral health (e.g., use of dentures, problems with teeth)
- Unintended movements in the extremities, mouth, or face and whether these movements are a bother or interfere with activities

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Patients should be instructed to sit in a chair with their feet flat on the ground; a general observation of the patient's body may be made at this point. Patients should also be asked to drape their arms over their legs, with their hands hanging over their knees. Several additional tasks should be done, including:

- Opening the mouth to observe whether the tongue is moving or at rest
- Sticking the tongue out to observe for any abnormal movements
- Tapping the thumb with each finger as rapidly as possible to observe the flexibility of fingers as well as any other body movements that occur while the patient is concentrating on this manual task
- Flexing and extending the arms and wrists one at }a time to monitor for rigidity and cogwheeling
- Walking around the room to observe for any parkinsonian-type movements

All findings during the examination should be recorded. It is important to note that repetitive, regular, rhythmic tremors are not recorded on the AIMS, as the tool is specific to tardive dyskinesia. However, these tremors may in fact be an adverse effect of neuroleptic treatment. If present, these movements should be monitored and considered when making treatment and pharmacotherapy decisions.

Metabolic Effects

Meta-analyses have shown that all antipsychotics are associated with an increased risk for weight gain, with the greatest gain seen with atypical agents (clozapine and olanzapine) and the least with typical agents (haloperidol). Numerous studies have concluded that H1 receptor antagonism action is most correlated with weight gain, although other receptor sites (including 5HT receptors) were also significantly associated with weight gain [21].

A reasonable approach to monitoring metabolic side effects involves measuring vital signs and weight prior to prescribing an antipsychotic agent and at every follow-up visit. Baseline blood work including a lipid profile, hemoglobin A1C, and a basic metabolic panel is also advised. Variances from baseline values and the presence or absence of weight gain can help guide the frequency of monitoring. However, obtaining laboratory studies at least yearly should be considered.

Cardiovascular Effects

Monitoring for QTc prolongation should be a consideration for all patients prescribed an antipsychotic. Obtaining a baseline electrocardiogram (EKG) prior to prescribing is good practice. Values greater than 500 msec should prompt referral to cardiology and a consideration to avoid medications that can prolong the QTc interval. Values of 450–500 msec require close follow-up EKG monitoring both after initiation of treatment and during any dosage adjustments.

ATYPICAL ANTIPSYCHOTICS

Antipsychotics remain a consistently popular option for the management of psychosis and schizophrenia. Since the reintroduction of clozapine in the 1990s, there has been a steady increase in the proportion of atypical antipsychotics prescribed compared with typical antipsychotics. By 2014, atypical antipsychotics accounted for almost 80% of total antipsychotics prescribed [22]. This has been partially attributed to treatment failure with typical antipsychotics (e.g., up to 30% of patients with schizophrenia fail to respond to typical antipsychotics), a desire to avoid extrapyramidal symptoms, and expansion of FDA-approved indications for atypical agents [17]. It should be noted that some of the lesser-used, low-potency typical antipsychotics may also avoid extrapyramidal effects.

As of 2021, there were 14 atypical antipsychotics approved for use in the United States (***Table 2***). Like the typical agents, these drugs are used primarily for the treatment of psychoses, although several are adjunctive treatments for major depressive disorder. Novel antipsychotics with various mechanisms of actions continue to be studied and approved; clinicians should consult the latest prescribing literature when selecting a medication for their patient.

When choosing an atypical antipsychotic, it is important that the clinician fully understand the mechanism of action of the drug being considered, as they have a wide variety of actions. There are also significant pharmacokinetic differences.

Aripiprazole

Aripiprazole is a partial dopamine agonist (not a blocker). Some research indicates that this medication may have a lower risk of tardive dyskinesia and metabolic syndrome. The initial effects of the oral preparation may be observed within days of treatment of bipolar disorder or acute mania and within one to two weeks in those with major depressive disorder or schizophrenia [19]. In all patients, continued improvement in efficacy is noted over the next several weeks. For bipolar/acute mania, maximal efficacy is seen in one to two weeks [19]. However, those with schizophrenia may see improvements for 4 to 6 weeks, and those with major depressive disorder may see maximal effects after 6 to 12 weeks [19].

Aripiprazole is metabolized hepatically and is primarily excreted in the feces (55%) and urine (25%). Peak plasma levels are noted in three to five hours following oral tablet administration, though high-fat meals can delay this time by hours. Following multiple IM doses of the extended-release formulation, peak plasma levels are noted in four days after deltoid administration or after five to seven days following gluteal administration [19].

ATYPICAL ANTIPSYCHOTIC MEDICATIONS					
Drug	**Dose Range**	**Typical Starting Dose**	**Usual Maintenance Dose[a]**	**Route(s)**	**Indication(s)**
Aripiprazole (Abilify)	2–30 mg/day	2.5–5 mg/day	10–20 mg/day	PO, decanoate	Bipolar disorder, treatment-resistant depression (adjunctive), schizophrenia
Asenapine (Saphris, Secuado)	5–10 mg BID	5 mg BID	10 mg BID	SL, transdermal patch	Bipolar disorder, schizophrenia
Brexpiprazole (Rexulti)	2–4 mg/day	1 mg/day	4 mg/day (with titration)	PO	Schizophrenia, treatment-resistant depression (adjunctive)
Cariprazine (Vraylar)	1.5–6 mg/day	1.5–6 mg/day	3–6 mg/day (with titration)	PO	Bipolar disorder, schizophrenia
Clozapine (Clozaril, Versacloz)	25–800 mg/day	25–800 mg/day	250–400 mg hourly or BID (Strict titration guidelines, must be in REMS)	PO (including oral disintegrating tablet)	Schizophrenia, suicidal behavior in schizophrenia or schizoaffective disorder
Iloperidone (Fanapt)	1–12 mg/day	1–2 mg BID	12 mg/day (lower doses in patients with hepatic dysfunction)	PO	Schizophrenia
Lumateperone (Caplyta)	42 mg/day	42 mg/day	42 mg/day	PO	Schizophrenia
Lurasidone (Latuda)	20–80 mg/day	20 mg/day	80 mg/day	PO	Bipolar major depression, schizophrenia
Olanzapine (Zyprexa)	2.5–20 mg/day	2.5–5 mg/day	15–20 mg/day	PO, IM, IV	Bipolar disorder, agitation/aggression associated with psychiatric disorders, schizophrenia
Paliperidone (Invega)	3–12 mg/day	3 mg/day	6 mg/day	PO, IM decanoate	Schizophrenia, schizoaffective disorder
Pimavanserin (Nuplazid)	34 mg/day	34 mg/day	34 mg/day	PO	Parkinson-associated psychosis
Quetiapine (Seroquel)	25–800 mg/day	50 mg/day	200–400 mg/day	PO, extended-release	Bipolar disorder, schizophrenia
Risperidone (Perseris, Risperdal)	0.5–6 mg/day	1–2 mg/day	4 mg/day	PO, IM decanoate	Bipolar disorder, schizophrenia
Ziprasidone (Geodon)	20–80 mg/day	40 mg BID	80 mg BID	PO, short-acting IM	Bipolar disorder (adjunctive), schizophrenia

[a]All dosing is for adults. For pediatric uses, consult pediatric-specific literature.
BID = twice daily, IM = intramuscular, IV = intravenous, PO = oral, QID = four times per day, REMS = Risk Evaluation and Mitigation Strategy, SL = sublingual.

Source: [17; 18; 19] *Table 2*

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The only absolute contraindication to the use of aripiprazole is hypersensitivity (including anaphylaxis) to the drug or any components of the formulation. The drug is associated with orthostatic hypotension and should be used with caution in patients predisposed to this effect or who are unable to tolerate transient hypotensive episodes [19]. Other possible adverse effects include increased serum glucose, weight gain, constipation, tremor, nausea/vomiting, agitation, anxiety, sedation/drowsiness, extrapyramidal reactions, headache, and insomnia [19].

Asenapine

What is the only atypical antipsychotic available in a sublingual formulation?

Asenapine is a dibenzo-oxepino pyrrole atypical antipsychotic with mixed serotonin-dopamine antagonist activity. It is unique as the only atypical antipsychotic available in a sublingual formulation. When administered sublingually for the management of agitation, the onset of effects is seen within 15 minutes. In bipolar disorder/acute mania, initial effects are present within days, with continued improvements over one to two weeks [19]. In patients being treated for schizophrenia, the initial effects are observed within one to two weeks, and maximal effects are noted in four to six weeks.

Asenapine is metabolized by the liver and excreted primarily in the urine and feces [19]. Peak plasma levels are attained within 0.5 to 1.5 hours for the sublingual formulation and within 12 to 24 hours for the transdermal patch.

Severe hepatic impairment (Child-Pugh class C) and hypersensitivity are considered absolute contraindications to asenapine. Possible adverse effects include drowsiness/fatigue, insomnia, extrapyramidal reactions, headache, weight gain, increased serum triglycerides and serum glucose, and oral hypoesthesia [19].

Brexpiprazole

Brexpiprazole exhibits partial agonist activity for 5-HT1A and D2 receptors and antagonist activity for 5-HT2A receptors. As a partial dopamine agonist, it is associated with a decreased risk for extrapyramidal reactions (including tardive dyskinesia) and metabolic syndrome. The onset of action for the oral formulation is typically within 1 to 2 weeks, with increased efficacy over the following weeks (4 to 6 weeks in those with schizophrenia and 6 to 12 weeks in those with major depressive disorder) [19].

Brexpiprazole undergoes hepatic metabolism, primarily by CYP3A4 and CYP2D6. It is excreted in the feces and urine. Brexpiprazole reaches peak plasma levels within four hours [19].

The only absolute contraindication to the use of brexpiprazole is hypersensitivity reactions. However, it should be used with caution in patients with renal impairment. The most common adverse effects of brexpiprazole are increased serum triglycerides (typically <500 mg/dL), weight gain, and akathisia (inability to remain still) [19].

Cariprazine

Cariprazine acts as a partial dopamine (D2) and serotonin (5-HT1A) agonist, with antagonist activity at serotonin 5-HT2A receptors. Onset of initial effects varies from days (with bipolar disorder/acute mania) to up to two weeks (with schizophrenia) [19]. As with the other atypical antipsychotics, effects increase over time to peak efficacy experienced in up to 12 weeks.

Cariprazine is extensively metabolized by CYP3A4 and, to a lesser extent, by CYP2D6 to active metabolites [19]. It is excreted through several routes, but most prominently through the urine. Peak plasma levels occur within three to six hours. Due to the long half-life of cariprazine and its active metabolites, changes in dose will not be fully reflected in plasma for several weeks.

There are no absolute contraindications to the use of cariprazine aside from hypersensitivity. Common adverse effects include extrapyramidal reactions, parkinsonian-like syndrome, akathisia, headache, nausea, and insomnia [19].

Clozapine

Clozapine has demonstrated efficacy in reducing the risk of suicide in patients with schizophrenia and known efficacy in treatment-resistant schizophrenia. It is believed to act through antagonism of the D2 and serotonin type 2A (5-HT2A) receptors [19]. The onset of action for the oral formulation is observed from within days up to two weeks, with increased effects for the subsequent weeks. For patients with treatment-resistant schizophrenia, longer trials of 8 to 12 weeks are recommended [19].

Metabolism of clozapine is extensively hepatic, with urinary and fecal excretion. Time to peak plasma levels is 2.2 to 2.5 hours, depending on the route of administration [19].

Serious hypersensitivity to clozapine or any component of the formulation is considered an absolute contraindication to its use [19]. Though not included in the U.S. labeling, Canadian labels include myeloproliferative disorders, impaired bone marrow function, active hepatic disease, severe renal impairment, paralytic ileus, uncontrolled epilepsy, severe nervous system dysfunction, and severe cardiovascular disease as additional contraindications. Common adverse effects are hypertension, hypotension, tachycardia, increased serum glucose levels, dyslipidemia, weight gain, constipation, decreased gastrointestinal motility, dyspepsia, nausea/vomiting, sialorrhea, dizziness, drowsiness/sedation, insomnia, vertigo, and fever [19].

The Clozapine REMS Program

Clozapine is associated with severe neutropenia (absolute neutrophil count [ANC] less than 500/mcL). The requirements to prescribe, dispense, and receive clozapine are incorporated into a single shared program called the Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program. A REMS is a strategy to manage known or potential risks associated with a drug or group of drugs and is required by the FDA for clozapine to ensure that the benefits of the drug outweigh the risk of severe neutropenia.

The Clozapine REMS Program provides a centralized point of access for prescribers and pharmacies to certify before prescribing or dispensing clozapine and to enroll and manage patients on clozapine treatment [23]. The monitoring requirements are established for the general population (most patients being prescribed clozapine) and for patients with benign ethnic neutropenia (BEN). BEN is a condition observed in certain ethnic groups whose average ANCs are lower than "standard" laboratory ranges for neutrophils. It is most commonly observed in individuals of African descent (approximate prevalence of 25% to 50%), some Middle Eastern ethnic groups, and in other non-White ethnic groups with darker skin; it is also more common in men [23]. At initiation of therapy, ANC monitoring should be conducted weekly for six months. If ANC levels remain ≥1,500/mcL in the general population or ≥1,000/mcL in patients with BEN, monitoring frequency may be reduced to every two weeks from 6 to 12 months, then monthly after 12 months. If neutropenia develops, monitoring may be more frequent, from three times weekly to daily depending on the severity of the neutropenia [23]. Prescribers are required to submit patients' ANC levels to the Clozapine REMS Program for every prescription of clozapine according to the patient's monitoring frequency.

Iloperidone

Iloperidone exhibits mixed dopamine (D2)/serotonin (5-HT2) antagonist activity. The agent's low affinity for histamine H1 receptors may decrease the risk for weight gain and somnolence, and its affinity for norepinephrine α1/α2C may improve cognitive function but increase the risk for orthostasis. With oral administration, the onset of antipsychotic action may be observed within one to two weeks of treatment, with four to six weeks to peak effect [19].

Hepatic metabolism of iloperidone results in creation of the active metabolites P88 and P95. These metabolites are excreted primarily in the urine and, less extensively, in the feces. Peak plasma levels are achieved in two to four hours [19].

Contraindications are limited to hypersensitivity reactions. The most common adverse effects are tachycardia, dizziness, drowsiness, increased serum prolactin, and weight gain [19].

Lurasidone

Lurasidone has documented mixed serotonin-dopamine antagonist activity, with high affinity for D2, 5-HT2A, and 5-HT7 receptors. Improvements in psychosis or bipolar disorder/depressive episode are noted within one to two weeks of treatment, although efficacy will improve for up to six weeks [19]. The medication should be given with food to improve absorption.

Hepatic metabolism is achieved primarily via CYP3A4 and results in two main active metabolites and two main nonactive metabolites [19]. Excretion is mainly in feces. Peak serum concentration occurs within one to three hours, with steady state concentrations achieved within seven days.

Lurasidone is contraindicated with hypersensitivity reactions or concomitant use with strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil) and inducers (e.g., rifampin, avasimibe, St. John's wort, phenytoin, carbamazepine) [19]. It should be used with caution and at the lowest possible dose in patients with hepatic impairment. Other common adverse effects include dyslipidemia, increased serum glucose, nausea, extrapyramidal reaction, drowsiness, akathisia, parkinsonian-like syndrome, and insomnia.

Olanzapine

Olanzapine displays potent antagonism of serotonin, dopamine, histamine, and alpha1-adrenergic receptors [19]. Its antipsychotic action is believed to be related to its effect on dopamine and serotonin. For acute agitation, effects are seen within 15 minutes with IM injection or within 5 to 10 minutes with IV administration. When administered orally for the management of bipolar disorder/acute mania or schizophrenia, initial effects are seen within days to two weeks; improvements may be noted for up to six weeks [19]. This agent is available in a long-acting injection formulation, and details about managing patients prescribed this route will be discussed in detail later in this course.

Olanzapine is metabolized via direct glucuronidation and cytochrome P450-mediated oxidation; 40% is removed via first-pass metabolism [19]. It is excreted in the urine (57%) and feces (30%). Maximum plasma concentrations after IM administration are five times higher than maximum plasma concentrations produced by an oral dose [19]. Clearance is increased in cigarette smokers and decreased in female patients. Following short-acting injection, peak plasma concentrations occur in 15 to 45 minutes; with extended-release injection, peak levels are noted in about one week. Following oral administration, peak serum concentrations are noted within six hours [19].

While there are no published contraindications to olanzapine, hypersensitivity is a likely barrier to use. This drug is associated with dose-related increases in prolactin levels, with associated menstrual-, sexual-, and breast-related effects [19].

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Adverse reactions seen most commonly include dyslipidemia, increased serum glucose, weight gain, increased appetite, xerostomia, decreased serum bilirubin, akathisia, dizziness, drowsiness/fatigue, extrapyramidal reactions, headache, insomnia, parkinsonism, and asthenia [19].

Quetiapine

As with the other atypical antipsychotics, the antipsychotic effects of quetiapine are believed to be the result of its antagonism of dopamine (D2) and serotonin (5-HT2) receptors [19]. It also has antagonistic action against 5-HT1A, D1, histamine (H1), and adrenergic alpha1- and alpha2-receptors, some of which may result in adverse effects. After oral administration, initial effects are seen within days (for bipolar disorder/acute mania or bipolar disorder/depressive episode) or up to two weeks (for schizophrenia). Continued improvement in symptoms should be expected for 1 to 12 weeks [19]. If the extended-release formulation is used in the management of generalized anxiety disorder, the initial effects are observed within four to seven days, with continued improvement for eight weeks.

Quetiapine metabolism is primarily hepatic, with mainly urinary elimination. The time to peak plasma level is 1.5 hours for the immediate-release version and 6 hours for the extended-release formulation [19].

There are no absolute contraindications to the use of quetiapine, aside from hypersensitivity. Drowsiness is a common effect and may be severe enough to result in impairment, inability to safely carry out activities of daily living (increased fall risk), and nonadherence [19]. Other common adverse effects include hypertension, orthostatic hypotension (particularly among elderly patients), tachycardia, dyslipidemias, weight gain, increased appetite, xerostomia, agitation, dizziness, extrapyramidal reaction, headache, and withdrawal syndrome.

Risperidone

Risperidone's high 5-HT2 and dopamine-D2 receptor antagonist activity is responsible for its antipsychotic action. However, alpha1, alpha2 adrenergic, and histaminergic receptors are also antagonized with high affinity. Onset of action is within days to 2 weeks, though peak effect may be experienced after up to 12 weeks [19]. An orally disintegrating tablet may be used to manage acute agitation, with 70 minutes mean time to calm.

Risperidone undergoes extensive hepatic metabolism to create the active metabolite 9-hydroxyrisperidone [19]. It is primarily excreted in the urine. Time to peak plasma level is about 1 hour with oral administration (but it is 3 to 17 hours for the active metabolite). When administered subcutaneously, the first peak is in 4 to 6 hours; the second peak is in 10 to 14 days.

Hypersensitivity to risperidone, paliperidone, or any component is an absolute contraindication. Following each subcutaneous injection, a lump may develop and persist for several weeks. This is a self-limiting effect, and the injection site should not be rubbed or massaged [19]. Other common adverse effects include hyperprolactinemia, weight gain, constipation, nausea/vomiting, upper abdominal pain, akathisia, anxiety, dizziness, drowsiness/fatigue, extrapyramidal reaction, headache, insomnia, parkinsonism, and tremor.

LONG-ACTING INJECTABLE ANTIPSYCHOTICS

A subset of antipsychotics (both typical and atypical) are available as long-acting injectable forms (***Table 3***). When prescribing a long-acting injectable antipsychotic, clinicians first initiate treatment with the oral form for a long enough period to demonstrate tolerance. The oral formulation should be continued until the long-acting therapy has been established. Both fluphenazine and haloperidol use sesame oil in their suspension, which may cause allergic reactions in patients sensitive to sesame.

There are no randomized controlled trials showing superiority of decanoate injections over other formulations; however, some small studies have shown at least similar efficacy of long-acting injected and oral haloperidol [24]. Plasma serum concentrations with steady-state decanoate yield lower plasma drug concentrations than with oral administration. This suggests that decanoate forms are at least as effective as oral agents and that lower doses may be effectively used with this formulation [24].

The efficacy of long-acting injectable antipsychotics other than haloperidol is not clear [25]. Studies have found varying results for different antipsychotics, both in terms of efficacy and side effect profile [24; 25]. The ultimate decision to select a long-acting injectable antipsychotic is complicated and typically driven by a need to improve compliance.

CLASS-WIDE ADVERSE EFFECTS AND WARNINGS

There are a variety of adverse effects and special population warnings that apply across the class of antipsychotic medications. These should be taken into account when selecting an agent, structuring the treatment plan, and conducting follow-up assessments.

Dementia-Related Psychosis

In general, the management of behavioral and psychological symptoms of dementia (most prominently psychosis and agitation/aggression) relies on the off-label use of atypical antipsychotics, along with any effective behavioral interventions. Unfortunately, these drugs are often less than clinically effective, with many patients displaying no or only partial response [26]. Furthermore, elderly patients with dementia are much more likely to experience the adverse effects of antipsychotics. The FDA has included a boxed warning

LONG-ACTING INJECTABLE ANTIPSYCHOTICS				
Drug	**Usual Dosing**	**Onset**	**Oral Overlap**	**Comments**
Fluphenazine decanoate	25 mg every 3 weeks	24 hours	24 hours	—
Haloperidol decanoate	50–200 mg every 4 weeks	One week	7 to 14 days	—
Paliperidone palmitate	117–156 mg monthly OR 273–819 mg every 3 months OR 1,092–1,560 mg every 6 months	—	None	Dosage will depend on the dose established prior to switching to the long-acting formulation. Maintenance dose started 3 weeks after dose 2.
Risperidone (Risperdal Consta)	12.5–25 mg every 14 days	7 days	3 weeks	—
Olanzapine (Zyprexa Relprevv)	300 mg every 4 weeks	7 days	None	Post-injection syndrome limits usage.
Aripiprazole	300–400 mg every 30 days	7 days	7 days	High cost may limit access.

Source: [19] *Table 3*

on the labels of all atypical antipsychotics regarding the increased mortality risk when these medications are used in elderly patients [26]. The APA recommends that non-emergency antipsychotic medication should "only be used for the treatment of agitation or psychosis in patients with dementia when symptoms are severe, are dangerous, and/or cause significant distress to the patient" [27].

Suicidality in Children, Adolescents, and Young Adults

Some antipsychotics are approved or used for the treatment of depressive episodes in bipolar disorder or as adjunctive treatment for unipolar depression. In this capacity, they are considered antidepressants, and antidepressants have been shown to increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (≤24 years of age) in the first months of treatment [28]. As such, a boxed warning has been added to the labeling information for these agents regarding this increased risk. This risk will be discussed in more detail later in this course.

Neuroleptic Malignant Syndrome

In patients taking antipsychotic medications, when might symptoms of neuroleptic malignant syndrome appear?

Neuroleptic malignant syndrome is a life-threatening idiosyncratic reaction to antipsychotic medications (including newer atypical agents, although it is more common with typical antipsychotics). It is a rare condition (occurring in approximately 0.01% to 0.02% of patients receiving antipsychotics), but it is unpredictable and potentially fatal, making it a significant concern [29]. Higher doses, higher potency, and long-acting formulations increase the risk of neuroleptic malignant syndrome.

Onset of symptoms is generally apparent within two weeks of treatment initiation. Clinical presentation consists of rigidity/stiffness, high fever, sweating, confusion, unstable blood pressure, and agitation. Signs and symptoms usually progress to a peak after three days. Prompt recognition is necessary to avoid significant morbidity and mortality, and treatment is immediate cessation of the antipsychotic medication and implementation of supportive measures (e.g., hydration, cooling) [30]. In more severe cases, administration of bromocriptine mesylate or dantrolene sodium may be indicated.

Elevated Prolactin Levels

An often-overlooked side effect of antipsychotics is elevated prolactin levels, which can present in men as gynecomastia or in women as galactorrhea and absence of menses. Elevated prolactin levels should be monitored and may necessitate changing agents.

Movement Disorders

As noted, extrapyramidal reactions can occur with antipsychotic therapy and can be a significant barrier to the effective use of these agents. There have also been anecdotal reports of dyskinesia seen with virtually all classes of medications, but the majority of patients with tardive dyskinesia have had exposure to antipsychotics. Studies estimate that up to 30% of patients on long-term antipsychotic therapy will develop various movement disorders [17; 31]. The risk is also elevated in elderly patients.

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The pathophysiology of tardive dyskinesia is believed to be related to abnormal functioning of the extrapyramidal tracks in the nervous system. Tardive literally means "late occurring," and although there are case reports of patients having symptoms after a single dose of a neuroleptic medication, the primary defining factor of tardive dyskinesia is that it is a later-occurring syndrome, as opposed to dystonia and akathisia, which usually develop in the early phases of treatment.

Tardive dyskinesia is also characterized by involuntary, uncontrollable movements. This differentiates it from dystonia, which is characterized by stiffness and decreased movement and can often be identified during AIMS testing by flexing the patient's wrists and elbows and observing for resistance. Akathisia is the perception of wanting to move and difficulty staying still; it often manifests as a constant need to pace or walk. In AIMS testing, akathisia can be identified in patients who have difficulty sitting without tapping feet, moving their legs, or otherwise having difficulties sitting still. Tardive dystonia typically presents with a fixed posturing of the face and neck, often a sideways tilt of the head, that the patient is unable to voluntarily correct. The most classic presentation of this is torticollis.

Proper diagnosis of movement disorders is essential, as treatment should be tailored to the specific disorder. Work-up of movement disorders should include consultation with appropriate specialists. This is especially important in the treatment of elderly patients for which the onset of parkinsonian movements may in fact be the hallmark of primary Parkinson disease as opposed to secondary parkinsonian side effects. Further assessment should be guided by neurologic consultation and may involve imaging.

After the specific movement disorder has been identified, treatment will focus on the goals of decreasing the movement disorder and the need to avoid destabilizing the patient's psychotic disorders.

Treatment of Tardive Dyskinesias

Treatment of tardive dyskinesia can be difficult and an impediment to the clinical stabilization of the patient. The primary consideration for patients receiving typical antipsychotics should be dose reduction or switching medications. Patients should be warned that tardive dyskinesia symptoms may initially worsen transiently as medication dosages are lowered (i.e., withdrawal-emergent dyskinesias). If a new medication will be used, clozapine should be considered first, as it has the lowest risk of tardive dyskinesia. However, it is vital to ensure that control of psychosis is maintained, particularly in patients at risk for self-harm or violence.

In 2017, the FDA approved the first medications for the treatment of tardive dyskinesia: valbenazine (Ingrezza) and deutetrabenazine (Austedo). The initial dose of valbenazine is 40 mg once daily. This is increased to 80 mg once daily after one week [19]. Continuation of a daily dose of 40 mg or 60 mg may be considered based on response and tolerability. Improvement is seen in 2 to 6 weeks, with the result stabilizing between 16 to 32 weeks. Deutetrabenazine is started at a dosage of 6 mg twice daily. This is increased as needed and tolerated in increments of 6 mg/day up to a maximum of 48 mg/day [19].

Although there is little evidence supporting this use, anticholinergics are often used to prevent extrapyramidal side effects caused by antipsychotics. Some clinicians will co-prescribe these drugs in an effort to prevent the development of extrapyramidal reactions. However, studies have shown that the numerous side effects associated with anticholinergics (e.g., cognitive impairment, urinary disturbances, vision changes, constipation) may preclude their use [31; 32]. Elderly patients are particularly vulnerable to these effects, and male patients older than 40 years of age are especially susceptible to acute urinary retention. The Canadian Psychiatric Association recommends that clinicians consider discontinuation of anticholinergic medications for the treatment of tardive dyskinesia, keeping in mind that there is very little evidence to support this course of action and that drug-induced parkinsonism may worsen [33]. If anticholinergics are used, they should be prescribed at the lowest possible dose, patients should receive education on the potential risks and benefits, and informed consent should be obtained.

RISK MITIGATION STRATEGIES

As discussed, risk mitigation strategies should be initiated when prescribing any antipsychotics. Although only clozapine has a formal REMS program, there are steps that should be taken with any antipsychotic prescription to minimize the potential for adverse effects and manage associated risks (***Table 4***).

Patients prescribed antipsychotics should receive education on the effects of the drugs, possible risks and benefits, and any recommended monitoring. However, this can be difficult if the patient has active psychosis or delusional paranoia. In these cases, caregivers and/or surrogate decision makers should be sought. All discussions should be fully documented. Patient education is an ongoing process (not a single event), and efficacy and adverse effects should be discussed regularly with patients as well as steps taken to treat or ameliorate adverse effects.

While ***Table 4*** presents an example of risk mitigation strategies for all antipsychotics, the actual strategies used should be specific to the patient and agent(s); abnormalities should generate a consult to appropriate medical team members. Aside from prevention and early detection of adverse effects, risk mitigation strategies should include a treatment plan for any possible adverse reactions. As discussed, there are several class-wide potential adverse effects, and these known risks should be reviewed and planned for.

RISK MITIGATION STRATEGIES FOR PATIENTS PRESCRIBED ANTIPSYCHOTICS	
Risk Mitigation Strategy	**Frequency of Assessment[a]**
AIMS testing	Every three months and after each dosage change
Electrocardiogram	One month after initiation, then yearly if QTc is less than 450 msec Recheck after any major dosage change
Weight	At each visit
Vital signs	At each visit
Laboratory studies[b]	With stable baseline values, consider monitoring every six months Recheck with any significant weight gain or symptoms
[a]All testing/assessment should occur prior to the initiation of therapy (to establish a baseline) and immediately after initiation. [b]Laboratory studies should include hemoglobin A1C, basic metabolic panel, complete blood count, and prolactin level.	
Source: Compiled by Author	*Table 4*

CASE STUDY

Patient A is 34 years of age with a history of schizoaffective bipolar disorder, first diagnosed at 18 years of age during his first year at college. His childhood was notable for several episodes of brief counseling for behavioral issues in school and at home, with a brief trial of methylphenidate (Ritalin) at 11 years of age. Patient A graduated from high school with his peers, but once at college, he developed delirious mania, paranoia, and psychosis. Treatment with olanzapine and valproic acid (Depakote) was initiated, but compliance has been an ongoing issue. During the past 16 years, the patient has had numerous episodes requiring hospitalization, one suicide attempt, and three arrests for breach of peace. He is now on probation and has been unable to maintain employment. He is living with his mother, who has communicated that he will have to leave the house if he does not take his medication. Patient A presents for medication management, stating that he does not like the weight gain he has experienced with many of the medications he has used in the past.

The nurse takes and documents a full history. On mental status exam, Patient A is alert and oriented. He scores 27 on a Mini-Mental State Exam (MMSE) and is mildly grandiose. His speech is slightly pressured but interruptible. At the time of presentation, Patient A is not taking any medications, having disagreed with his last provider's prescription of olanzapine, a drug that had been effective in the past.

Patient A is 6 feet 1 inch tall and weighs 235 pounds. His blood pressure is 124/86 mm Hg. Laboratory studies are requested, and all return normal. An EKG reveals a normal QTc and sinus rhythm.

The nurse asks Patient A what he wants to gain in his medication management, and his stated goals are to continue to live with his mother, to avoid future arrest, and to be able to maintain a job. The nurse discusses available typical and atypical oral and decanoate antipsychotics. After a long discussion, Patient A decides to try long-acting injection risperidone (Risperdal Consta). Patient education includes the risks of extrapyramidal reactions (e.g., movement disorders), weight gain, and prolactin elevation, which can lead to gynecomastia, as well as risk mitigation strategies if any of these develop.

A baseline AIMS test is conducted and is negative for any existing issues. The oral trial of risperidone is initiated, as required before using any long-acting injectable to demonstrate tolerance. The patient is titrated up to an oral dosage of 3 mg twice daily, which appears to resolve the patient's paranoia, pressured speech, and hypomania. Patient A reports that he is functioning better, but he reiterates that he does not think he will be able to comply with daily oral medication. The decision is made to progress to long-acting injected risperidone, which requires a three-week overlap with the oral medication.

While there is no exact dosage equivalency, the manufacturer recommends that a 6-mg total oral daily dose of risperidone should be converted to a bimonthly injectable dose of 37.5–50 mg long-acting risperidone. The patient is started at 37.5 mg IM every two weeks. After three weeks, the patient is stable and able to wean off the oral risperidone, decreasing to 4 mg in two divided doses for three days, then 2 mg in divided doses for three days, before total cessation. During this time, the nurse maintains frequent contact with Patient A to verify stability and compliance.

After six weeks, laboratory studies are ordered, including blood glucose level, lipids, and prolactin level, and a repeat EKG is done. All findings are normal. The nurse continues to administer the AIMS test every three months and to check weight and vital signs at every visit. While Patient A continues with this therapy, laboratory values are rechecked every three to six months.

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Patient A responds well to treatment and is able to remain living with his mother. After six months, he has gained employment at a fast food restaurant and has avoided any contact with law enforcement.

ANTIDEPRESSANT MEDICATIONS

Depressive disorders affect approximately 17.3 million, or 1 in 6, Americans each year [34; 35; 36]. Major depressive disorder is present in approximately 22.2 million American adults, or about 7% of the U.S. population 18 years of age and older in a given year. The lifetime incidence of depression in the United States is 20% in women and 13% in men, or about 17% of all Americans.

There are five major classes of antidepressants available in the United States: tricyclic antidepressants (TCAs), MAOIs, SSRIs, serotonin-noradrenaline reuptake inhibitors (SNRIs), and atypical antidepressants (***Table 5***). Modern antidepressants were introduced in the 1950s following serendipitous discovery of antidepressant effects with TCAs and MAOIs. SSRIs were introduced in the late 1980s, followed by atypical antidepressants and SNRIs [37]. The monoamine hypothesis, proposed to explain the unexpected effects of TCAs/MAOIs in the 1950s, posits that depression results from deficient brain serotonin and/or norepinephrine levels. This remained the dominant paradigm of depression and the basis of nearly all FDA-approved antidepressants for the next five decades [38; 39]. However, limitations of the monoamine hypothesis and mechanistic homogeneity of standard antidepressants are now understood. Major depressive disorder is more complex and diverse than previously assumed, and novel pathways that underlie its pathophysiology have been identified [40; 41].

Unlike psychotic disorders, first-line therapy for mild depression should include nonpharmacologic interventions, such as cognitive behavioral therapy, guided self-help, interpersonal psychotherapy, and other lifestyle and psychosocial interventions. Evidence-based guidelines recommend that the process of treatment selection involve shared decision making between provider, patient, and family members, and that the values, priorities, and goals of the patient be included in discussions of risks and benefits of treatment options [42]. Ongoing communication with other providers involved in the care of a patient is essential for coordination and monitoring and can involve different care providers in the same primary care clinic or the primary care provider and therapist or psychiatrist [43].

Combining pharmacotherapy and psychotherapy treatments should be considered for patients with major depressive disorder when practical, feasible, available, and affordable. Both approaches combined show better outcomes than either as monotherapy. When unable to combine therapy because of patient preference or problems with availability or affordability, consider psychotherapy when the presentation is mild-to-moderate, and antidepressants when depression is severe or chronic [44]. Patients with major depressive disorder with psychotic features should receive an antipsychotic and an antidepressant medication or ECT. Lithium can be added in patients unresponsive to antipsychotic/antidepressant therapy [43]. Other specific factors should be considered in treatment planning, including the presence of substance abuse, specific features, and other comorbid disorders. If a patient displays signs of potential suicide, increasing the treatment intensity, including hospitalization if needed, should be considered, and pharmacotherapy and psychotherapy should both be provided [43].

Prior to the prescription of antidepressants, patients should have a full history and physical exam and any relevant medical conditions (e.g., heart failure, renal disease) should be noted. A full medication reconciliation should be conducted, with special attention to potential interactions.

Treatment with antidepressant medications can involve dosage adjustments and/or trials of a different medication at some point to maximize response and minimize side effects [43]. Patient adherence to the medication regimen is essential in achieving the maximum clinical benefit. Providers should closely monitor patients for worsening depressive symptoms and emergent suicidality; appropriate intervention includes stopping or modifying the drug therapy or hospital admission [44]. Providers should instruct patients and caregiver(s) to be alert for emerging agitation/irritability, suicidality, and worsening depression, and to report this immediately to a healthcare provider [44].

The treatment efficacy of antidepressants in major depressive disorder is broadly similar. Other factors to help guide medication selection include previous patient or family member response to antidepressants (if any); impact on psychiatric or medical comorbidities; clinician familiarity; patient preference; safety in overdose; availability and cost; and drug-drug interactions [44]. Most second-generation antidepressant drugs are recommended as first-line treatment due to the quality of published data, side effect tolerability, and safety in overdose relative to TCAs and MAOIs [43; 44; 45].

The three most distressing side effects for patients treated with antidepressants are sleep disturbance, sexual dysfunction, and weight gain [46]. Choice of medication should be guided by knowledge of comparative side effects and patient priorities; some patients will be more concerned about sexual side effects, while for others, nausea, sleep disturbances, or weight gain may be more distressing [47]. In addition, available evidence regarding the optimal pharmacotherapeutic selection for the treatment of dimensions of depression and DSM-5 specifiers should be considered.

ANTIDEPRESSANT MEDICATIONS[a]				
Drug	**Dose Range**	**Typical Starting Dose**	**Potential Adverse Effects**	**Comments**
MAOIs				
Selegiline (Emsam, Zelapar)	6–12 mg transdermal patch every 24 hours	6 mg transdermal patch every 24 hours	Serious food and drug interactions	Also used in treatment of Parkinson disease
Isocarboxazid (Marplan)	10–40 mg/day	10 mg BID		May take 3 to 6 weeks to see effects. Dose should be reduced once maximum clinical effect is seen. If no response obtained within 6 weeks, additional titration is unlikely to be beneficial.
Phenelzine (Nardil)	15–30 mg every 8 hours	15 mg every 8 hours		—
Tranylcypromine (Parnate)	10–60 mg BID	10–30 mg BID		—
Moclobemide	300–600 mg/day	300 mg/day in 2 divided doses		—
Tricyclic Antidepressants				
Amitriptyline	50–300 mg/day	25–50 mg/day as a single dose at bedtime or in divided doses	Xerostomia, sedation	Follow levels and EKG/QTc
Clomipramine (Anafranil)	12.5–250 mg at night	12.5–50 mg at night		Approved for OCD, off-label for MDD
Doxepin (Silenor)	25–300 mg at night or in divided doses	25–50 mg at night		Usually reserved for treatment-resistant MDD
Imipramine	25–300 mg at night or in divided doses	25–50 mg at night or in divided doses		—
Trimipramine	25–300 mg at night or in divided doses	25–50 mg at night or in divided doses		—
Amoxapine	25–600 mg total (may be BID dosing)	25–50 mg at bedtime or BID		The maximum dose in outpatients is 400 mg/day; in hospitalized patients, it is 600 mg/day.
Desipramine (Norpramin)	25–300 mg daily or in divided doses	25–50 mg/day		—
Nortriptyline (Pamelor)	25–150 mg/day	25 mg at night		—
Protriptyline	10–60 mg daily divided in 3 to 4 doses	10–20 mg daily divided in 3 to 4 doses		—

Table 5 continues on next page.

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ANTIDEPRESSANT MEDICATIONS[a] *(Continued)*				
Drug	**Dose Range**	**Typical Starting Dose**	**Potential Adverse Effects**	**Comments**
SSRIs				
Citalopram (Celexa)	20–40 mg/day	20 mg/day	GI upset	Few drug interactions Lower maximum daily dose (20 mg) recommended for patients at risk for QTc prolongation
Escitalopram (Lexapro)	10–20 mg/day	10 mg/day	GI upset	Also approved for generalized anxiety disorder
Fluoxetine (Prozac)	20–80 mg/day	20 mg/day	GI upset, activation syndrome	Also approved for bulimia, panic disorder, generalized anxiety disorder, OCD, and PMDD
Fluvoxamine, immediate-release	50–300 mg at night	50 mg at night	Nausea	Approved for OCD, off-label for MDD
Fluvoxamine, controlled-release	100–300 mg at night	100 mg at night		
Paroxetine (Brisdelle, Paxil, Pexeva)	20–50 mg/day	20 mg/day	Sedation	Also approved for generalized anxiety disorder, panic disorder, OCD, PTSD, PMDD, social anxiety disorder, and vasomotor symptoms of menopause
Paroxetine, controlled-release (Paxil CR)	25–62.5 mg/day	25 mg/day	Sedation	
Sertraline (Zoloft)	50–200 mg/day	50 mg/day	GI upset	Also approved for OCD, panic disorder, PMDD, PTSD, and social anxiety disorder
SNRIs				
Venlafaxine (Effexor)	37.5–375 mg BID	37.5–75 mg BID	Nausea, hypertension, xerostomia, drowsiness	Use with caution in patients with glaucoma
Venlafaxine, extended-release (Effexor XR)	37.5–225 mg/day	37.5–75 mg/day	Nausea, xerostomia, hypertension	Use with caution in patients with glaucoma Also approved for generalized anxiety disorder, panic disorder, and social anxiety disorder
Levomilnacipran (Fetzima)	20–120 mg/day	20 mg/day	Orthostatic hypotension (dose related), nausea	—
Desvenlafaxine (Pristiq)	50–100 mg/day	50 mg/day	Dizziness, insomnia, hyperhidrosis, nausea, xerostomia, anxiety	No evidence that dosing over 50 mg is more effective In patients who are sensitive to side effects (particularly anxiety), consider lower starting dose (25 mg/day)

Table 5 continues on next page.

ANTIDEPRESSANT MEDICATIONS[a] *(Continued)*				
Drug	**Dose Range**	**Typical Starting Dose**	**Potential Adverse Effects**	**Comments**
Duloxetine (Cymbalta, Drizalma Sprinkle)	40–120 mg/day	40–60 mg/day	Activation syndrome, weight loss, GI upset, headache	Also approved for fibromyalgia, generalized anxiety disorder, chronic musculoskeletal pain, and diabetic neuropathic pain Avoid in patients with renal impairment (CrCl <30 mL/min)
Milnacipran (Savella)	25–100 mg BID	25–50 mg BID	Nausea, headache, constipation, insomnia	Approved for fibromyalgia, off-label for MDD
Atypical Antidepressants				
Bupropion (Aplenzin)	75–450 mg/day in divided doses	100 mg BID	Increased seizure threshold, weight loss, GI upset, agitation	Also approved for smoking cessation and seasonal affective disorder No sexual side effects
Bupropion, sustained-release (Wellbutrin SR)	150–200 mg BID	150 mg/day in the morning		
Bupropion, extended-release (Forfivo XL, Wellbutrin XL)	150–450 mg/day in the morning	150–175 mg/day in the morning		
Mirtazapine (Remeron)	15–45 mg at bedtime	15 mg at bedtime	Weight gain, increased appetite, drowsiness	Weight gain may limit satisfaction and compliance
Trazodone	50–600 mg BID	50 mg BID	Drowsiness, dizziness, xerostomia, GI upset	—
Nefazodone	50–600 mg in divided doses	50–100 mg BID	Headache, xerostomia, drowsiness	Should not be initiated in individuals with active liver disease or elevated baseline serum transaminases
Brexanolone (Zulresso)	—	60-hour continuous IV infusion (Total dose: 270 mg/kg)	Drowsiness, sedation, xerostomia, dizziness	Used only for inpatient treatment of postpartum depression Requires REMS
Esketamine (Spravato)	56–84 mg intranasal twice weekly	56–84 mg intranasal twice weekly	Dissociation, anxiety, nausea, dizziness	Reserved for treatment-resistant MDD or MDD with suicidality Requires REMS

Table 5 continues on next page.

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ANTIDEPRESSANT MEDICATIONS[a] *(Continued)*				
Drug	**Dose Range**	**Typical Starting Dose**	**Potential Adverse Effects**	**Comments**
Multimodal Agents				
Vilazodone (Viibryd)	10–40 mg/day	10 mg/day	Headache, GI upset	Alternative agent
Vortioxetine (Trintellix)	5–20 mg/day	5–10 mg/day	Nausea, sexual dysfunction	

[a]All information provided is for reference only. Unless otherwise stated, all agents are approved for the treatment of major depressive disorder, unipolar.
BID = twice daily, EKG = electrocardiogram, GI = gastrointestinal, MAOI = monoamine oxidase inhibitor, MDD = major depressive disorder, OCD = obsessive-compulsive disorder, PMDD = premenopausal dysphoric disorder, PTSD = post-traumatic stress disorder, SNRI = serotonin and norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

Source: [17; 19] *Table 5*

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

What are advantages of using SSRIs in the treatment of depression?

SSRIs are thought to act by inhibiting serotonin transporters (SERT) that reuptake serotonin (5-HT) into the presynaptic cell, increasing 5-HT in the synaptic cleft. SSRIs have advantages of low overdose lethality and better tolerability than first-generation antidepressants, which can improve adherence. SSRIs are particularly effective in patients with obsessive-compulsive symptoms, but may initially worsen anxiety or panic symptoms [35; 43; 44]. This class includes the agents fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), fluvoxamine (Luvox), citalopram (Celexa), escitalopram (Lexapro), and vortioxetine (Brintellix). Escitalopram may have fewer drug-drug interactions than other SSRIs, and fluoxetine may be a better choice in patients with poorer adherence due to its long half-life [35; 43; 44].

Common Side Effects

The most common side effects with SSRIs are gastrointestinal (nausea, vomiting, and diarrhea), activation/insomnia (restlessness, agitation, anxiety, akathisia, and sleep disturbances), sexual, headache, fatigue, and weight gain [35; 43; 44]. Many of these side effects dissipate over time. Sertraline is particularly associated with diarrhea, and paroxetine with weight gain [35; 43].

SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS

SNRIs act by inhibiting the reuptake of the neurotransmitters serotonin and norepinephrine. This results in an increase in the extracellular concentrations of serotonin and norepinephrine and therefore an increase in neurotransmission [35; 43; 44]. Most SNRIs, including venlafaxine (Effexor), desvenlafaxine (Pristiq), levomilnacipran (Fetzima), and duloxetine (Cymbalta), are several-fold more selective for serotonin than norepinephrine.

Safety, tolerability, and side effect profiles of SNRIs resemble SSRIs, with the exception that the SNRIs have been associated (rarely) with sustained elevated blood pressure. SNRIs can be used as first-line agents, particularly in patients with significant fatigue or comorbid chronic pain, and have an important role as second-line agents in patients who have not responded to SSRIs [35; 43; 44].

Venlafaxine is especially beneficial in treating anxiety and panic attacks in patients with depression, and acts like an SSRI at lower doses (75 mg/day) but more like an SNRI at doses ≥150 mg/day [35; 43; 44].

Common Side Effects

SNRIs are associated with greater likelihood of increased pulse rate, dilated pupils, dry mouth, excessive sweating, and constipation [44]. Venlafaxine has a greater incidence of nausea and vomiting than SSRIs and may be associated with an increased risk for cardiovascular events [35; 43].

TRICYCLIC ANTIDEPRESSANTS

TCAs are predominantly serotonin and/or norepinephrine reuptake inhibitors that act by blocking the serotonin transporter and the norepinephrine transporter, respectively, which results in an elevation of the extracellular concentrations of these neurotransmitters, and therefore an enhancement of neurotransmission. TCAs also have varying but typically high affinity for the H1 and H2 histamine receptors and muscarinic acetylcholine receptors. As a result, they also act as potent antihistamines and anticholinergics. These properties are generally undesirable in antidepressants, however, and likely contribute to their large side effect profiles [48].

TCAs are classified by the nature of the final amine group on the side chain, with the tertiary amines amitriptyline (Elavil), clomipramine (Anafranil), doxepin (Sinequan), trimipramine (Surmontil), imipramine (Tofranil), and lofepramine (Lomont); the secondary amines nortriptyline (Pamelor), desipramine (Norpramin), and protriptyline (Vivactil); and the tetracyclic antidepressants amoxapine (Asendin) and maprotiline (Ludiomil).

TCAs are comparable in efficacy to SSRIs/SNRIs, but their side effect profile makes them seldom used as first-line therapy [35; 43; 44]. TCAs may initially worsen anxiety or panic symptoms. Due to side effect potential of cardiac arrhythmia, TCAs should be used very cautiously, if at all, in patients with heart problems. Secondary amine TCAs cause less orthostatic hypotension and sedation than tertiary amines, which should be avoided in elderly patients due to the risk for orthostatic hypotension, sedation, cognitive problems, and cardiac effects. The secondary amine nortriptyline is especially effective for elderly patients with moderate-to-severe depression. Clomipramine is particularly effective in patients with obsessive-compulsive symptoms [35; 43; 44].

Common Side Effects

Anticholinergic and antihistamine activity accounts for many side effects, including dry mouth, blurred vision, reduced gastrointestinal motility or constipation, urinary retention, cognitive and/or memory impairment, and increased body temperature [35; 43; 44]. Other side effects may include drowsiness, anxiety, emotional blunting (apathy/anhedonia), confusion, restlessness, dizziness, akathisia, hypersensitivity, changes in appetite and weight, sweating, sexual dysfunction, muscle twitches, weakness, nausea and vomiting, hypotension, tachycardia, and arrhythmia. Tolerance to side effects often occurs if treatment is continued. Side effects may also be less troublesome if treatment is initiated with low doses and gradually increased [48; 49].

MONOAMINE OXIDASE INHIBITORS

MAOIs inhibit monoamine oxidase (MAO), an enzyme that degrades and inactivates 5-HT, norepinephrine, and dopamine. This increases monoamine levels and activity. Earlier MAOIs were irreversible MAO inhibitors, deactivating the enzyme until slowly replenished over a two-week period [50; 51]. MAOIs includes phenelzine (Nardil), tranylcypromine (Parnate), isocarboxazid (Marplan), linezolid (Zyvox, Zyvoxam, Zyvoxid), moclobemide (Aurorix, Manerix), pirlindole (Pirazidol) (approved for use in parts of Europe), and selegiline (Deprenyl, Eldepryl, Emsam).

Most MAOIs appear broadly effective in a range of depressive and anxiety disorders, and may be more effective than other antidepressant classes in major depressive disorder with pronounced anxiety or panic symptoms [35; 43; 44]. Major depressive disorder with atypical features may preferentially respond to MAOIs over other antidepressant classes. Although effective, MAOIs are rarely the first- or second-line treatment choice due to serious side effect potential from medication interactions and dietary restriction. The selegiline transdermal patch (Emsam) used at the lowest strength (6 mg delivered over 24 hours) may lack the dietary restrictions required of oral MAOIs [52].

Common Side Effects

With oral ingestion, MAOIs inhibit the catabolism of dietary amines. When foods containing tyramine are consumed, the individual may suffer from hypertensive crisis [50]. If foods containing tryptophan 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.

MAOIs should not be combined with psychotropic drugs or with any other psychoactive substance except under expert care. This includes a wide range of prescribed, over-the-counter, and illicit drugs and nutritional supplements, such as St. John's wort. Common side effects include orthostatic hypotension, weight gain, sexual dysfunction, sedation, headache, and insomnia [50].

ATYPICAL ANTIDEPRESSANTS

The atypical antidepressants are diverse in monoamine activity and do not fit the profile of other classes. They include bupropion (Wellbutrin), nefazodone (Serzone), mirtazapine (Remeron), and trazodone (Desyrel). Nefazodone and trazodone block postsynaptic serotonin type-2 receptors and inhibit presynaptic serotonin reuptake. Bupropion inhibits activity of norepinephrine and dopamine transporters, and the active metabolite hydroxybupropion contributes to the drug's effects. Mirtazapine is a potent antagonist at 5-HT2, 5-HT3, alpha2, and H1 histamine receptors. As a group, these agents show low toxicity in overdose and may have an advantage over the SSRIs by causing less sexual dysfunction and gastrointestinal distress [35; 43; 44].

Each agent has apparent benefits and drawbacks, with some better suited for specific patient populations. Bupropion is associated with a risk of seizure at higher doses, especially in patients with a history of seizure or eating disorders, and should be used cautiously in anxious patients [35; 43; 44]. It may be more effective for atypical major depressive disorder than other antidepressants.

Mirtazapine can be very sedating and promotes appetite and weight increase, which in some patients may be desirable. It has a faster onset of action than fluoxetine, paroxetine, or sertraline, and may be superior to SSRIs in depression associated with severe insomnia and anxiety. Trazodone is also very sedating and is usually used as a sleep aid rather than as an antidepressant [35; 43; 44].

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Common Side Effects

The side effects of atypical antidepressants vary considerably. With bupropion, the most common side effects are agitation, jitteriness, mild cognitive dysfunction, insomnia, gastrointestinal upset, and possible increased risk for seizures [35]. Patients taking mirtazapine may experience dry mouth, sedation, weight gain, and increased serum cholesterol [43]. Sedation is the most common side effect associated with trazodone, followed by cardiovascular side effects (such as orthostasis) and sexual side effects [43]. Finally, nefazodone is associated with sedation, dry mouth, nausea, constipation, orthostasis, visual alterations, and possible increased risk of hepatotoxicity; this has led to nefazodone being seldom prescribed [35].

MULTIMODAL ANTIDEPRESSANTS

Vilazodone and vortioxetine are multimodal antidepressants that combine SSRI properties with other pharmacologic actions affecting monoamine and non-monoaminergic targets. Evidence does not suggest greater efficacy than SSRI/SNRIs, but these agents may improve tolerability or efficacy on specific clinical domains [53].

Vilazodone, approved in 2011, primarily acts as a SERT inhibitor and 5-HT1A receptor partial agonist, and modestly inhibits dopamine and norepinephrine transporters. This antidepressant may be most helpful in patients lacking response to initial SSRIs. Vilazodone must be taken with food, which increases its absorption and bioavailability by 72% [54; 55].

Vortioxetine, approved in 2013, acts through various serotonin receptors as an antagonist (5-HT3/7/1D), partial agonist (5-HT1B), or agonist (5-HT1A), and inhibits SERT. It also activates the glutamate system in the frontal cortex. Vortioxetine displays a specific clinical efficacy in the treatment of cognitive deficits associated with major depressive disorder. The most common side effects are nausea, vomiting, and constipation [53].

CLASS-WIDE ADVERSE EFFECTS

Sexual Dysfunction

All commercially available antidepressants are associated with sexual side effects. SSRI/SNRIs show the highest rates of sexual dysfunction, including impaired sexual motivation, desire, arousal, and orgasm affecting men and women. Prescribers greatly underestimate the prevalence and patient burden of sexual side effects from antidepressants and other medications [56]. Among antidepressants, prevalence rates of sexual side effects are highest with venlafaxine and SSRIs; moderate with TCAs and MAOIs; low with bupropion, trazodone, nefazodone, mirtazapine, agomelatine, and vilazodone; and lowest with the reversible MAOI moclobemide [57; 58]. Compared to spontaneous patient reporting, systematic inquiry increases the rate of identifying sexual side effects by ≥60% [58].

Management of sexual side effects in men includes the use of phosphodiesterase-5 inhibitors such as sildenafil, vardenafil, tadalafil, and avanafil as first-line treatment or switching to bupropion [59]. In women, sexual side effect management considers symptoms, age, and potential hormonal contribution when peri- or post-menopausal.

Increased Suicidality

Several papers documenting an increased risk of suicidal thoughts and behavior with antidepressants, primarily SSRIs, have been published over the past decade. A review of the literature found that antidepressant use, including SSRIs, carried a small short-term risk of inducing suicidal thoughts and suicide attempts in persons younger than 25 years of age, with persons 30 to 40 years of age having a lower risk than those younger than 25 years. This risk should be balanced against the well-known beneficial effects of antidepressants that include reduced suicidal ideation and behavior, particularly in the long term. Clinical decision making should weigh the benefits and potential risks and strive to keep the potential risks of antidepressant treatment to a minimum [60; 61].

Discontinuation Symptoms

Antidepressant discontinuation (more appropriately termed withdrawal) symptoms are described by the FINISH mnemonic (flu-like symptoms, insomnia, nausea, imbalance, sensory disturbances, hyperarousal), may be experienced by up to 40% of patients when antidepressants are stopped abruptly, and may occur with any antidepressant [62; 63; 64; 65]. SSRI withdrawal symptoms are far more frequent with paroxetine. Common symptoms include dizziness, nausea, headache, confusion, low energy, weakness, sleep disturbance, flu-like symptoms, restlessness, agitation, anxiety, panic, anger, and irritability. Less common and more severe symptoms include electric-shock sensations, vertigo, paresthesia, intensified suicidal ideation, aggression, derealization, depersonalization, and visual/auditory hallucinations. Gradual tapering is a reasonable strategy but does not prevent the onset of SSRI withdrawal [66]. SSRI withdrawal syndrome is least likely with fluoxetine and vortioxetine [62].

Symptoms usually begin within five days of treatment cessation or occasionally during taper or after missed doses [67; 68]. Symptoms may be severe enough to interfere with daily functioning, and although a four-week taper is usually suggested, some patients may require longer periods, particularly with paroxetine and venlafaxine [69]. Treatment is pragmatic. If symptoms are mild, reassure the patient that this is a common occurrence and that the symptoms will pass in a few days. If symptoms are severe, reintroduce the original antidepressant or a replacement from the same class with a longer half-life, and taper gradually while monitoring for symptoms. Patients should be emphatically informed that the possible or actual emergence of discontinuation symptoms is not a manifestation of addiction to the antidepressant [70]. SSRI withdrawal can also be approached by switching to a course of fluoxetine, such as 10 mg for several weeks, which is slowly tapered and discontinued [43].

PEDIATRIC CONSIDERATIONS

Among the antidepressants, only fluoxetine is approved for use in treating major depressive disorder in pediatric patients. In addition, fluoxetine, sertraline, fluvoxamine, and clomipramine are approved for obsessive-compulsive disorder (OCD) in pediatric patients. Other than these indications, all other use of antidepressants in children is off-label [71]. However, these off-label uses are relatively common, particularly among adolescents and pediatric patients with more severe disease.

Beginning in 2003, data have suggested an increase in attempted and completed suicides in children treated with antidepressants [72]. There is also compelling research indicating that the decrease in prescribing of antidepressant medications to adolescents in the period after 2003, both in the United States and the Netherlands, led to an increase in suicide rate [72]. In the Netherlands, the rate increased by 49% between 2003 and 2005, during which time there was a significant decrease in pediatric SSRI prescriptions.

Data for pediatric efficacy (defined as improvements in depressive symptoms) are strongest for fluoxetine, which is approved for children older than 8 years of age [72]. The best results are achieved with a combination of pharmacotherapy and cognitive-behavioral therapy. Due to the risks and complexities involved in the treatment of children with depression, it is recommended that a multidisciplinary team approach be utilized in the treatment of these patients.

Pediatric patients being treated with antidepressants for any indication should be closely observed for clinical worsening, as well as agitation, irritability, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. This monitoring should include daily observation by families and caregivers and frequent contact with the physician. It is also recommended that prescriptions for antidepressants be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose [71].

TREATMENT-RESISTANT DEPRESSION

What are contributors to treatment-resistant depression?

Standard antidepressants fail to produce adequate response in 30% to 50% and remission in up to 70% of patients with major depressive disorder [73; 74; 75]. Partial response, instead of full remission, leaves patients with impairing residual symptoms and high risk of relapse. Each relapse increases symptom severity, decreases treatment response, and heightens risk of treatment-resistant depression [76].

Treatment-resistant depression is a problem increasingly encountered by primary care and mental health providers. Contributors to treatment-resistant depression include illness severity, medical and psychiatric comorbidity, and the limitations of FDA-approved drug options. The definition of treatment resistance lacks consensus, but the most common definition is an inadequate response to two or more antidepressants. This does not consider adjunctive strategies or distinguish patients with partial versus non-response [62; 77].

The American Psychiatric Association recommends optimizing the medication dose as a reasonable first step for patients treated with an antidepressant who have not responded fully to treatment if the side effect burden is tolerable and the upper limit of a medication dose has not been reached.

(https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Last accessed July 7, 2020.)

Strength of Recommendation: II (Recommended with moderate clinical confidence)

In addition to augmentation strategies, a diverse and growing range of interventions are available as options for treatment-resistant depression [78; 79; 80]. Most engage novel therapeutic targets.

Neurostimulation Therapies

The limitations of standard antidepressants, frequent treatment resistance, and the paradigm shift in psychiatry away from specific neurotransmitter focus and toward an integrative neural network perspective has prompted the development of novel depression treatment approaches, such as neurostimulation therapy. Repetitive transcranial magnetic stimulation (rTMS) is a nonpharmacologic approach to the treatment of depression approved in 2008, and multiple randomized controlled studies have shown its use to be safe and effective [81]. Patient selection for rTMS is complex and should be done in conjunction with the specialist administering the therapy as well as the patient. Most clinicians refer patients after they have failed to improve on at least one antidepressant.

Electroconvulsive Therapy

The use of ECT in the treatment of treatment-resistant depression is long and varied. While there was historical misuse and abuse of this modality, particularly in the unethical care of patients in institutions, it has a proven record of efficacy for patients with severe or refractory depression.

ECT is effective as acute treatment, but multiple treatments are required and many who respond experience symptoms again within six months [82]. ECT generates electrical stimuli for seizure induction through electrodes applied to the scalp, with the patient under general anesthesia and pre-medicated with a muscle relaxant. Clinical outcomes are highly influenced by electrode placements, electrical intensity, and pulse width [83].

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As first-line treatment, ECT is used for severe melancholic, catatonic, psychotic, or refractory depression and for patients who refuse to eat or drink, have very high suicide risk or severe distress, pregnant women with severe depression, or who have a previous positive ECT response [47; 82; 84].

Full ECT response requires at least four to six sessions delivered two to three times per week. Twice weekly ECT requires longer treatment duration, but more than three treatments per week is not recommended due to the greater cognitive side effect risk [83].

Headaches (45%), muscle soreness (20%), and nausea (1% to 25%) during ECT are transient and treated symptomatically; 7% of patients with major depression switch into a manic or mixed state [83]. Most distressing to some patients is loss of autobiographic memory recall, infrequently reported to persist beyond six months [84]. ECT lacks absolute contraindication, but increased safety risk is associated with space-occupying cerebral lesion, increased intracranial pressure, recent cerebral hemorrhage, or aneurysm [83; 85].

Pharmacotherapy

Ketamine is an *N*-methyl-D-aspartate receptor (NMDA-R) antagonist that was approved for use as an anesthetic in 1970. Demonstration that a single IV dose in patients with treatment-resistant depression reliably produced rapid, robust antidepressant effects for one week was a breakthrough discovery for research and a turning point for patients for whom all other treatment approaches had failed [86]. The short-term efficacy of ketamine treatment of refractory major depressive disorder and bipolar depression is now established; more than one dozen placebo-controlled trials have shown that patients with refractory unipolar or bipolar depression have significantly greater response, remission, and depressive symptom reduction to single-dose IV ketamine than placebo from 40 minutes through days 10 to 12 post-treatment [87; 88]. The approach has become standardized, using a sub-anesthetic dose: 0.5 mg/kg IV over a 40-minute infusion. In a 2015 analysis, ketamine was designated as one of two psychiatric treatments that had the highest potential impact on patient outcomes. This designation was based on the serious unmet need for fast-acting, well-tolerated antidepressants with efficacy in refractory major depression and bipolar depression [40].

In 2019, a ketamine derivative—esketamine—was approved by the FDA as an adjunctive agent for treatment-resistant depression. In 2020, the additional indication for short-term treatment of suicidal thoughts was added. This agent is administered by nasal spray and must be given under the direct supervision of a healthcare provider. Patients should be monitored for adverse effects for at least two hours following administration [19; 89]. Due to an increased potential for abuse and misuse, it has an associated REMS program.

CASE STUDY

Patient B, 46 years of age, presents with a history of mild-to-moderate depression for the past six months. He has been undergoing cognitive-behavioral therapy, and while he has made some gains, he continues to experience depressive symptoms, as documented by a mood map and reports from his therapist. In addition, he is overweight and complains of insomnia.

The nurse does a complete psychiatric history and orders baseline laboratory studies and EKG. The patient reports no history of suicidal ideation and has never been hospitalized. He states that he is functioning well in his job but has been unable to maintain a steady relationship, despite a desire to have a long-term partner.

Patient B's main complaints are depressed mood and insomnia. He does not endorse anxiety or panic attacks and denies any drug or tobacco use. The patient is relatively healthy, has received regular medical care, and does not take any other medications. He has no history of seizure disorder. After a long discussion with the patient, the nurse decides to start a trial of sertraline 50 mg/day and trazodone 25 mg at night.

Patient B returns in two weeks and reports that his sleep has improved and the medications are well tolerated. He agrees to return in four more weeks to determine if the medications are helping his mood, which currently has not improved. During that period, he will continue working with his therapist weekly. The nurse and therapist are in good communication, with an understanding that any changes in symptoms or tolerability should be shared immediately.

After four weeks, Patient B comes back to the office. His mood is still described as depressed by both him and his therapist, so the sertraline dosage is increased to 100 mg/day, with a plan for the patient to return in one month.

When Patient B returns in four weeks, he reports that he is feeling better and has been going out and socializing. However, he is experiencing sexual side effects (erectile dysfunction). Several options are discussed, including transitioning from sertraline to a trial of bupropion or adding a trial of sildenafil. The patient decides that he would like to switch to bupropion, because he does not like the idea of having to take another medication.

After decreasing the dose of sertraline to 50 mg for two weeks, the patient is stable and plans are made to discontinue the sertraline and start bupropion (Wellbutrin XR) 150 mg every morning. When Patient B presents in two weeks, he is happy with the new medication, reporting full resolution of the sexual side effects, but reports some residual depressed mood. The dose of bupropion is increased to 300 mg every morning.

In another four weeks, Patient B's depression is in remission and his sleep quality is significantly improved. The medications remain well-tolerated. The patient also notes that he has lost about 5 pounds, which he attributes to decreased appetite. The patient continues to work with his therapist and agrees to return monthly for at least the next three months for continued monitoring.

MOOD STABILIZERS AND BIPOLAR DISORDER

What is the typical starting dose for lithium in the treatment of bipolar disorder?

Perhaps no diagnosis in psychiatry has undergone such a rapid change in diagnostic standards and pharmacologic management as bipolar disorder in the last 30 years. Intravenous chlorpromazine was first noticed to decrease mania in surgical patients with bipolar disorder. Shortly thereafter, chlorpromazine and other antipsychotics became mainstays in the treatment of primary psychotic disorders. At the same time, the treatment of bipolar disorder was revolutionized by the discovery of lithium.

Lithium is perhaps the oldest drug still in clinical use. While its utilization was formally standardized in 1954, its use in psychiatry dates to the mid-19th century [6]. One of the earliest recorded medical uses of lithium, for the treatment of gout, was in 1847 in London. Lithium continued to be prescribed for the treatment of gout and renal calculi into the 1930s. Psychiatric interest in lithium can be traced to the late 1800s. William Hammond is believed to be the first physician to prescribe lithium for mania (in 1871) [6]. As noted, the United States was the 50th country to approve lithium for clinical use in 1970 [6]. Lithium was originally studied in the prevention of depression and continues to be used off-label as an antidepressant [6; 90].

Today, management of bipolar disorder may consist of lithium, anticonvulsants, and/or antipsychotic medications (***Table 6***). Antianxiety medications may be prescribed short term to improve sleep and manage agitation/anxiety. Lithium is one of the few drugs used in the treatment of bipolar disorder with proven efficacy in the prevention of suicide [79].

EVIDENCE-BASED PRACTICE RECOMMENDATION

When using any psychotropic medication for bipolar disorder, the National Collaborating Centre for Mental Health recommends that clinicians ensure that the person is given information that is suitable for their developmental level about the purpose and likely side effects of treatment including any monitoring that is required, and give them an opportunity to ask questions. The choice of medication is made in collaboration with the person with bipolar disorder, taking into account the carer's views if the person agrees. The overall medication regimen is regularly reviewed so that medications that are not needed after the acute episode are stopped.

(https://www.nice.org.uk/guidance/cg185. Last accessed September 28, 2021.)

Level of Evidence: Expert Opinion/Consensus Statement

CASE STUDY

Patient C, 23 years of age, presents with a history of increasing mood instability, with periods of depression lasting three to four months followed by periods of increasing disorganization, lack of need for sleep, and risky behaviors (e.g., gambling, shoplifting). After her third shoplifting arrest, Patient C agreed to a plea deal that requires her to seek and comply with psychiatric care.

The clinician conducts a full psychiatric history that is significant for school and employment problems. She attempted outpatient treatment at 16 and 21 years of age, both of which were ended by the patient due to her dislike for medications and their side effects and a perceived "loss of energy" when treatment was initiated with olanzapine during a manic episode at 19 years of age.

The workup reveals a healthy woman, normal laboratory studies, normal EKG, and no medical problems. She is gravida 0 para 0 and has a progestin intrauterine device for birth control. She describes her current mood as depressed, rated 3 on a Likert scale. She describes hypersomnia, sleeping about 10 hours per day. She is currently unemployed and living with her parents. She denies any psychotic symptoms and has never attempted suicide. The patient feels her parents are supportive but firm in stating that she must engage in treatment to continue living with them. She is a nonsmoker and has no known drug use, other than occasional cannabis (less than once per week), which she does not view as problematic. She has genetic loading, with an uncle and a sister who have been diagnosed with bipolar disorder.

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MEDICATIONS USED IN THE TREATMENT OF BIPOLAR DISORDER				
Drug	**Dose Range**	**Typical Starting Dose**	**Potential Adverse Effects**	**Comments**
Lithium (Lithobid)	600–1,800 mg/day in divided doses	300 mg BID	Xerostomia, tremor, thyroid-stimulating hormone elevation, leukocytosis, nausea	Lithium toxicity is closely related to serum lithium levels and can occur at doses close to therapeutic levels. Monitoring should be available before initiating therapy.
Anticonvulsants				
Valproic acid (Divalproex)	250–1,500 mg BID based on levels	250–500 mg PO BID	Weight gain, hair loss, GI upset	Drug levels, complete blood count, and hepatic function should be followed.
Carbamazepine (Carbatrol, Epitol, Equetro, Tegretol)	100–800 mg BID	100–200 mg BID	Weight gain	Hepatic function, drug level, and CBC should be followed.
Lamotrigine (Lamictal, Subvenite)	Titrate to maximum 200 mg/day	25 mg/day	Nausea, tremor, rash, Stevens Johnson syndrome	—
Atypical Antipsychotics				
Aripiprazole (Abilify)	2.5–30 mg/day	2.5–5 mg/day	Weight gain (least likely in this class), extrapyramidal symptoms, constipation, sedation	Available in long-acting IM formulation
Asenapine (Saphris, Secuado)	2.5–10 mg BID	2.5–5 mg PO BID	Weight gain, extrapyramidal symptoms, constipation, sedation	—
Cariprazine (Vraylar)	1.5–6 mg/day	1.5 mg/day	Weight gain, extrapyramidal symptoms, constipation, sedation	—
Lurasidone (Latuda)	40–160 mg/day	40 mg/day	Weight gain, extrapyramidal symptoms, constipation, sedation	—
Olanzapine (Zyprexa)	2.5–30 mg either BID or at night	2.5 mg/day	Weight gain (very likely), extrapyramidal symptoms, constipation, sedation	—
Olanzapine/fluoxetine (Symbyax)	Up to 18 mg/day olanzapine and 75 mg/day fluoxetine	6 mg/day olanzapine and 25 mg/day fluoxetine	Weight gain, extrapyramidal symptoms, constipation, sedation	Usually given at night
Quetiapine (Seroquel)	50–800 mg/day	50–100 mg daily or BID	Weight gain, extrapyramidal symptoms, constipation, sedation	Available in extended-release formulation
Risperidone (Perseris, Risperdal)	0.5–6 mg/day (may be given BID)	0.5–1 mg daily or BID	Weight gain, extrapyramidal symptoms, constipation, sedation, increased prolactin, male gynecomastia	Available in long-acting IM formulation
Ziprasidone (Geodon)	40–80 mg BID	40 mg BID	Weight gain, extrapyramidal symptoms, constipation, sedation, increased prolactin	Taken with food to improve absorption
BID = twice per day, CBC = complete blood count, GI = gastrointestinal, IM = intramuscular, PO = oral.				
Source: [19; 80]				*Table 6*

Patient C is currently not seeing a therapist or receiving psychotherapy. In discussing goals of care, her main goal is compliance with her probation stipulations. She also indicates that she would like to be employed and to eventually move out of her parents' house. Weight gain is identified as an intolerable side effect of pharmacotherapy; the patient states she would like to lose weight. After much discussion, Patient C agrees to see a social worker for cognitive support and to assist with employment goals.

Given the patient's goals and concerns, antipsychotics are determined to be undesirable. The clinician and patient discuss the risks and benefits of valproic acid and lithium. Patient C states that her uncle did well on lithium and that she would like to try it. In preparation for lithium prescription, the patient's thyroid hormone and calcium levels are reviewed along with kidney function; all are normal. Patient C expresses a strong desire to take pills only once per day and does not think she can remember to take a morning dose. The clinician reviews literature, which indicates that once daily dosing of lithium results in similar efficacy, with lower total doses, decreased renal toxicity, and decreased urinary frequency [91]. The patient is started on controlled-release lithium 450 mg taken at night. Eventually, she is titrated to 900 mg daily, with an average serum lithium level of 0.7 mEq/L.

As part of the patient education process, the clinician emphasizes the need for reliable birth control, as lithium crosses the placenta and is associated with serious fetal malformations following exposure in the first trimester [92]. This conversation is documented fully, including a recommendation that the patient use dual birth control (e.g., add condoms). The need to use a different medication during any planned pregnancy is reviewed.

After 12 months of therapy, Patient C has not experienced any episodes of mania. However, she describes her mood as depressed and complains of amotivation, sadness, hypersomnia, and a 10-pound weight gain. Her lithium level is stable and within the therapeutic range, and the clinician is concerned that raising the lithium dose could increase the risk of toxicity.

To address these issues, bupropion (Wellbutrin XL) 150 mg/day is added to the patient's regimen. Augmentation with low-dose bupropion appears to have the lowest risk of inducing mania among available antidepressants [93]. In six weeks, Patient C reports a gradual improvement in mood, a slight weight loss (2 to 3 pounds), and no signs or symptoms of mania. She continues to meet with her social worker and has attained employment as a front desk clerk at a hotel. She is pursuing her goal of living independently and has had no further contact with law enforcement.

ANTIANXIETY MEDICATIONS

Anxiety disorders are characterized by states of chronic, excessive dread or fear of everyday situations. The fear and avoidance can be life-impairing and disabling. Anxiety disorders result from the interaction of biopsychosocial factors, whereby genetic vulnerability interacts with situations, stress, or trauma to produce clinically significant syndromes. Under the umbrella of anxiety disorders are specific phobia, social anxiety disorder, panic disorder, agoraphobia, generalized anxiety disorder, and separation anxiety disorder.

Each year in the United States, anxiety disorders impact approximately 42 million adults, or 19% of the population [94; 95]. The pattern of sex distribution is consistent among anxiety disorders, and the overall female-to-male ratio is approximately 2:1 across all age ranges [96]. Guidelines for the treatment of anxiety disorders typically support combined psychotherapy (e.g., mindfulness, exposure therapy, cognitive therapy) and pharmacotherapy [97].

The first report of antidepressant use in anxiety treatment was published in 1962. In this account, patients with agoraphobia who were given the TCA imipramine showed reductions in panic attacks and improved exposure to feared situations [98]. The benzodiazepine chlordiazepoxide (Librium) was introduced to the U.S. market in 1960. This was followed by diazepam (Valium) in 1963, which became the most prescribed drug in the United States from 1969 to 1982; in 1978, more than 2.3 billion diazepam doses were sold in the United States [99]. Panic disorder was first formalized as a psychiatric disorder in the 1980 DSM-III, and alprazolam (Xanax) became the first FDA-approved drug for panic disorder treatment in 1981, remaining the most-prescribed benzodiazepine to date [100].

In the past two decades, antidepressant drugs have displaced benzodiazepines as the most widely prescribed and recommended anxiety disorder pharmacotherapy (***Table 7***). Antidepressants are generally recommended as first-line therapy for panic disorder because, unlike benzodiazepines, antidepressants treat comorbid depression and lack abuse risk and potential side effects of excessive sedation, cognitive impairment, and ataxia. All major antidepressant classes are comparably effective, but SSRIs and, increasingly, SNRIs are recommended over TCAs and MAOIs due to better safety and tolerability [101].

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MEDICATIONS USED IN THE TREATMENT OF ANXIETY DISORDERS				
Drug	**Dose Range**	**Typical Starting Dose**	**Potential Adverse Effects**	**Indication(s)**
Antidepressants				
Escitalopram (Lexapro)	10–20 mg/day	10 mg/day	Few	GAD
Fluoxetine (Prozac)	10–80 mg/day	10–20 mg/day	Few	OCD, PD
Fluvoxamine	100–300 mg/day	100 mg/day	Few	OCD, SP
Paroxetine (Brisdelle, Paxil, Pexeva)	10–50 mg/day	10–20 mg/day	Few	GAD, OCD, PD, SP
Sertraline (Zoloft)	25–200 mg/day	25–50 mg/day	Few	OCD, PD, SP
Duloxetine (Cymbalta, Drizalma Sprinkle)	30–120 mg/day	30–60 mg/day	Hypertension, headache	GAD
Venlafaxine (Effexor)	37.5–225 mg/day	37.5–75 mg/day	Hypertension, headache	GAD, PD, SP
Clomipramine (Anafranil)	25–250 mg/day	25 mg/day	QTc prolongation	OCD, PD
Doxepin (Silenor)	25–300 mg/day	25–50 mg/day	QTc prolongation	NSA
Imipramine	50–200 mg/day	50–100 mg	QTc prolongation	PD
Phenelzine (Nardil)	45–90 mg/day	45 mg/day	Drug- and food-drug interactions	PD
Benzodiazepines				
Alprazolam (Xanax)	0.25–4 mg 2 to 3 times per day	0.25–1 mg/day	Dependence, rebound anxiety, increased dementia risk, increased risk of opioid overdose with concomitant use	NSA, PD
Chlordiazepoxide (Librium)	5–25 mg 3 to 4 times per day	5–10 mg/day		NSA
Clonazepam (Klonopin)	0.25–2 mg 2 times per day	0.25–1 mg/day		PD
Diazepam (Diastat, Valium, Valtoco)	2.5–10 mg 2 to 4 times per day	2.5–5 mg/day		NSA
Lorazepam (Ativan)	0.5–2 mg given 2 to 3 times per day	0.5–1 mg/day		NSA
Miscellaneous Agents				
Hydroxyzine (Vistaril)	25.5 mg 2 to 4 times per day	25–50 mg/day	Xerostomia, drowsiness	NSA
Buspirone	10–20 mg 2 to 3 times per day	10 mg/day	Dizziness, headache	GAD

GAD = generalized anxiety disorder, NSA = nonspecific anxiety, OCD = obsessive-compulsive disorder, PD = panic disorder, SP = specific phobia.

Source: [19; 102] *Table 7*

ANTIDEPRESSANTS

Although all major antidepressant classes are comparably effective against anxiety disorders, which class is recommended due to better safety and tolerability?

SSRIs are considered first-line therapy for generalized anxiety disorder and panic disorder [101; 103]. TCAs have comparable efficacy to SSRIs in panic disorder and generalized anxiety disorder [104; 105]. TCAs are lethal in overdose and, compared with SSRIs, have a markedly broader, more problematic, and less tolerable side effect profile [101]. Nonetheless, TCAs may work when first-line agents do not [106]. Also, some patients with panic disorder are sensitive to both beneficial and adverse effects of TCAs, so cannot tolerate imipramine doses >10 mg/day but still experience panic blockade [101].

MAOIs are effective for panic disorder and social anxiety disorder and are thought by some to be superior options for severe, treatment-resistant anxiety disorders. As noted, MAOIs have a substantial side effect profile and impose the greatest safety burden of all antidepressants. Therefore, they are usually reserved as the last treatment option after other drug therapies have failed to achieve remission [107]. Clinicians do not routinely prescribe MAOIs for anxiety disorders, although they are probably not considered often enough in treatment-resistant patients [106].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The National Collaborating Centre for Mental Health asserts that all patients prescribed antidepressants for the management of anxiety should be informed that, although the drugs are not associated with tolerance and craving, discontinuation/withdrawal symptoms may occur on stopping or missing doses or, occasionally, on reducing the dose of the drug.

(https://www.nice.org.uk/guidance/cg113. Last accessed September 28, 2021.)

Level of Evidence: Expert Opinion/Consensus Statement

BENZODIAZEPINES

Since their introduction in the early 1960s, benzodiazepines have been the most prescribed drugs for anxiety over the majority of the past half-century. Although SSRI/SNRI agents have replaced benzodiazepines as the top-prescribed anxiolytics, benzodiazepine prescribing remains common. In 2016, alprazolam and lorazepam were among the top 25 most frequently prescribed psychotropic medications in the United States; alprazolam ranked second, and lorazepam ranked ninth [108; 109].

Pharmacology and Short-Term Effects

Numerous benzodiazepines are available and have similar pharmacodynamic properties and clinical actions; they mainly differ in pharmacokinetic properties (absorption, distribution, metabolism, elimination). Benzodiazepines bind to a specific receptor site in the gamma-aminobutyric acid (GABA) receptor complex. GABA is the primary inhibitory neurotransmitter in the central nervous system, and benzodiazepines cause non-selective GABA-A inhibitory effects throughout the brain that include drowsiness, cognitive impairment, dampening of fear and anxiety, memory impairment, anticonvulsant actions, and impairment of balance, motor control, muscle tone, and coordination. Adverse reactions to alprazolam also include amnesia, aggression, mood changes, and hostility. The newer Z drugs (e.g., zolpidem, zopiclone) have similar actions to benzodiazepines but are marketed for insomnia due to their pharmacokinetic profile, with high doses required for anxiolytic effects. There is evidence the Z drugs share similar risks to benzodiazepines [110; 111].

Meta-analyses suggest alprazolam, lorazepam, and diazepam are effective but comparable in generalized anxiety disorder efficacy, while clonazepam shows much greater efficacy in the treatment of panic disorder than alprazolam, lorazepam, and diazepam, which all have modest efficacy [112].

Appropriate Prescribing

Benzodiazepine treatment of anxiety disorders is controversial. While effective in rapid anxiety reduction, the potential drawbacks with long-term use are substantial. These agents are indicated when potent, short-term anxiolytic effects are necessary to permit infrequent exposure to feared stimuli and potentially severe anxiety, such as airplane travel [103; 106; 113]. Clonazepam, lorazepam, and alprazolam are effective for short-term use in panic disorder, generalized anxiety disorder, and SAD, but ineffective for, and potentially worsening, comorbid depression [114]. The rapid anxiolytic effects make benzodiazepines highly appealing to patients with anxiety, but aside from this specific context, benzodiazepine prescribing for as-needed use is discouraged [106; 115; 116]. Benzodiazepines can reinforce pill taking, serve as a safety signal that undermines self-efficacy, and become incorporated into conditioned fear responses; these concerns are heightened with as-needed use. On-demand dosing links pill taking to rapid anxiety reduction, powerfully reinforcing avoidance in anxiety-provoking situations and encouraging longer-term reliance on the drug. This iatrogenic effect also contributes to poor response to cognitive-behavioral therapy.

The current recommended prescribing is for time-dependent use, instead of panic response-dependent use, to minimize the risks [103]. This would also seem to maximize risk of withdrawal syndrome from uninterrupted versus intermittent drug exposure.

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Benzodiazepines are also useful in the initial weeks of SSRI/SNRI initiation to rapidly reduce anxiety and possible early anxiogenic medication side effects before the onset of SSRI/SNRI anxiolytic effects [103; 106; 113]. However, patients may discontinue the antidepressant when co-prescribed a rapidly effective benzodiazepine, believing the benzodiazepine's symptom relief makes the SSRI/SNRI unneeded. Supportive therapy with regular visits or phone contacts may also help patients remain adherent until the delayed onset of antidepressant benefits appears or early antidepressant side effects lessen [117].

Another indication for benzodiazepine use is for the short-term relief (two to four weeks only) of anxiety that is severe, disabling, or subjecting the individual to unacceptable distress. Perhaps the greatest prescribing challenge with benzodiazepines is preventing short-term use from insidiously developing into long-term use. Patients with the most severe anxiety may obtain the greatest relief and become most hesitant to discontinue use [118]. In many cases, clinicians ignore the recommended two- to four-week prescribing limit, mainly because alternative options with superior anxiolytic effects are not available [119]. Clinicians intending to prescribe alprazolam should carefully consider the likelihood that its use will remain restricted to the very short term—a few days to a couple weeks—to see the patient through a crisis [118].

Benzodiazepines may be prescribed to augment SSRI/SNRI therapy for improved response in select patients with significant residual anxiety or non-response. In one study, patients with SAD and sertraline nonresponse after 10 weeks were given sertraline plus clonazepam (≤3 mg/day), venlafaxine (≤225 mg/day), or sertraline plus placebo for 12 weeks. Those with sertraline augmented by clonazepam showed greatest reduction in SAD symptoms and a better overall response rate than comparator groups, although remission rates did not differ significantly [120]. These agents are third- or fourth-line treatment in patients unresponsive or intolerant to other anxiolytic drugs who remain highly symptomatic [103; 106; 113]. Generally, patients with a history of substance abuse, personality disorder, or chronic pain should not be treated with benzodiazepines because of the high risk for overuse of these medications [113]. While benzodiazepines should usually be reserved for patients lacking response to at least two treatments (i.e., non-response to an SSRI/SNRI and a psychologic treatment), concerns about potential problems in long-term use should not prevent their use in patients with persistent, severe, distressing, and impairing anxiety symptoms [121].

It seems the most appropriate guidance for benzodiazepine prescribing involves occasional, context-specific use or cautious use during SSRI/SNRI initiation [121; 122]. Otherwise, benzodiazepines should be reserved for patients lacking response to three or more treatments, such as an SSRI, an SNRI, and a psychologic intervention, who remain highly symptomatic.

Risks/Drawbacks

While alprazolam remains the most-prescribed benzodiazepine for anxiety disorders, evidence suggests that relative to other benzodiazepines, alprazolam is no more effective and may have specific drawbacks [100]. Alprazolam may have greater potential for dependence than other benzodiazepines due to its rapid onset of anxiolysis and short half-life. With the short half-life, persons prescribed fixed-interval alprazolam (e.g., every six to eight hours) can experience morning withdrawal symptoms following the last nighttime dose. This is frequently mistaken as relapse in anxiety for which the drug was originally prescribed, confirming the continuing need for the drug [118]. The alprazolam product monograph states that such emergence of interdose symptoms reflect insufficient plasma levels, best managed by adding the same dose for four times daily administration (but breakthrough anxiety and alprazolam withdrawal are not differentiated). The document also states that alprazolam treatment of panic disorder differs from sub-syndromal anxiety, in that recommended dosing is as close to around-the-clock as possible, or three or four times per day [123].

Long-term benzodiazepine use can result in added symptoms during stable-dose maintenance, including increasing anxiety and withdrawal-associated symptoms such as perceptual disturbances and paresthesia. This emerging withdrawal syndrome despite ongoing benzodiazepine use is much more likely with highly potent and rapidly eliminated alprazolam or lorazepam and is temporarily alleviated by dose escalation. As craving, dysphoria, and other withdrawal symptoms develop over time between doses, the motivation to continue benzodiazepine use for anxiolysis gradually merges with the need to avoid withdrawal symptoms [124].

Benzodiazepine prescriptions are associated with nonmedical use and the development of benzodiazepine use disorder unrelated to co-occurring drug use or anxiety disorder diagnosis/severity [109]. Acute cognitive-impairing side effects are drowsiness, increased reaction time, ataxia, motor incoordination, and anterograde amnesia. In one study, long-term use of an average 17 mg/day diazepam equivalent led to substantial cognitive decline that did not resolve three months after cessation [125]. Motor vehicle accident risks during benzodiazepine therapy are comparable to driving with a blood alcohol concentration of 0.050% to 0.079% [126]. Hip fracture risk is increased by ≥50% in older persons who take benzodiazepines; with zolpidem, the risk is increased 200% in persons older than 65 years of age [127]. The risk of overdose is particularly great when benzodiazepines are combined with sedative drugs such as opioids or alcohol.

Personality traits associated with long-term use, emotional dependence, and more severe/protracted benzodiazepine withdrawal have been described. Long-term benzodiazepine users often have poor stress coping abilities. Benzodiazepines compensate for these deficits, but their use interferes with learning stress coping strategies, including behavioral therapy

for agoraphobia. Passive-dependent personality traits and lack of internal and external stress coping resources increases vulnerability to withdrawal symptoms and motivation for continued use. In these patients, benzodiazepine deprivation renders them unprotected from stress and re-exposes their coping deficits. Chronically anxious people have been found innately hypersensitive to punishing stimuli and punishment; benzodiazepines can be described as "depunishing" drugs [124].

Withdrawal

Despite comparable dosing, patients with which anxiety disorder often show greater difficulty tapering off of benzodiazepines?

Withdrawal symptoms following benzodiazepine cessation are appropriately concerning and a liability of this drug class that all prescribers should understand. In patients with panic disorder discontinuing alprazolam following 1.5 to 22 months of treatment, 33% to 100% were unable to completely taper [43]. These data did not include the 50% of long-term benzodiazepine users who do not consent to withdrawal studies or who later quit the study. The experience of benzodiazepine withdrawal is known to deter patients from future attempts [128]. An estimated 25% to 76% of patients prescribed benzodiazepines are long-term users. Defining high-dose benzodiazepine varies, but users of high-dose benzodiazepines commonly have comorbid disorders and are unlikely to benefit from current discontinuation and withdrawal strategies that expose them to greater risk of impairment and injury [128].

Despite comparable dosing, patients with panic disorder often show greater difficulty tapering than patients with generalized anxiety disorder. Problems during alprazolam tapering are most severe during the last half of the taper. Patients with panic disorder receiving diazepam or alprazolam had fewer problems during taper of the top 50% of daily dose. However, with abrupt discontinuation of the remaining dose, alprazolam caused significantly more anxiety, relapse, and rebound. This may reflect greater problems withdrawing from short half-life, high-potency benzodiazepines like alprazolam [43].

CASE STUDY

Patient D, 33 years of age, presents with a chief complaint of anxiety. He describes increasing anxiety symptoms for the last eight months, including persistent worrying that he finds challenging to control, overthinking plans, inability to let go of a worry, difficulty concentrating, fatigue, difficulty falling asleep, irritability, and nervousness. He is employed as a corrections officer with two young children. A medical workup is normal. He has engaged with a therapist for the past three months, and while he has made some gains with cognitive-behavioral therapy, his therapist has suggested a medication consultation to help with his ongoing symptoms.

Upon review of symptoms and consultation with the patient's therapist, a diagnosis of generalized anxiety disorder is confirmed. The clinician discusses goals of care with the patient; he states that he wants to avoid the medication side effects of daytime sedation or impaired concentration due to his job. Available medications are reviewed, and the decision is made to start escitalopram to address the continued symptoms of generalized anxiety. Treatment is initiated at a daily dose of 10 mg. Patient D asks about alprazolam (Xanax), as a friend told him that this medication worked for him. The clinician spends time on patient education explaining that alprazolam has a known risk of addiction and a potential for sedation. The patient agrees to the trial of escitalopram.

When Patient D returns for follow-up in four weeks, he reports improvement in his anxiety symptoms and is continuing his cognitive-behavioral therapy. After three months, the patient indicates that his symptoms are manageable and he has not experienced any adverse effects of the pharmacotherapy.

PHARMACOTHERAPY FOR SUBSTANCE USE DISORDERS

Which agents are approved for the treatment of alcohol use disorder?

Although perhaps the most concerning drug of abuse in the United States today is opioids, substance use disorders (as defined by the DSM-5) are not limited to one specific drug. Even commonly used substances, such as alcohol and nicotine, may initiate use disorders. Substance use disorders are diagnosed based on the presence of at least two of the following criteria in the previous year [129]:

- Using the substance in larger amounts
- Wanting to cut down use but unable to
- Spending large amounts of time involved in procuring and using as well as recovering from use of the substance
- Cravings for the substance
- Not functioning normally at work, home, or school
- Continued use despite harm to relationships
- Decreasing other activities, including work or socialization
- Continued use despite harm or risk of harm
- Continued use despite medical or psychological problems made worse by continued use
- Increased tolerance leading to escalating dosages
- Withdrawal symptoms

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MEDICATIONS USED IN THE TREATMENT OF SUBSTANCE USE DISORDERS				
Drug	**Dose Range**	**Typical Starting Dose**	**Potential Adverse Effects**	**Route(s)**
Opioid Use Disorder				
Buprenorphine/naloxone (Bunavail, Suboxone, Zubsolv)	Buprenorphine: 0.7–24 mg/day Naloxone: 0.18–6 mg/day	4/1 mg/day	Pain, headache, nausea, diaphoresis	Buccal film, sublingual film, sublingual tablet
Methadone (Dolophine, Methadose, DISKETS)	20–120 mg/day	20–30 mg/day	Pruritus, constipation, cardiac abnormalities	PO, IV
Naltrexone (Vivitrol)	PO: 25-50 mg/day IM: 380 mg/week	PO: 25 mg/day IM: 380 mg/week	Injection site reactions, anxiety, syncope	PO, IM
Buprenorphine (Belbuca, Buprenex, Butrans, Probuphine, Sublocade)	SQ: 100–300 mg/month SL: 2–24 mg/day	SQ: 300 mg/month Implant: 4 implants SL: 2–4 mg/day	Few	Sublingual tablet, subdermal implant, SQ injection
Alcohol Use Disorder				
Acamprosate (Campral)	666 mg TID	666 mg TID	Diarrhea	PO
Naltrexone (Vivitrol)	PO: 25–100 mg/day IM: 380 mg/month	PO: 50 mg/day IM: 380 mg/month	Injection site reactions, anxiety, syncope	PO, IM
Disulfiram	125–500 mg/day	250 mg/day	Bitter taste, impotence, drowsiness	PO
Nicotine Use Disorder				
Bupropion, sustained-release (Zyban)	150 mg daily or BID	150 mg/day	Weight loss, constipation, agitation, xerostomia, nausea	PO
Nicotine	Gum: Up to a maximum 30 pieces/day Inhaler: 6–16 cartridges/day Lozenge: Titrate to 1 lozenge every 4 to 8 hours Nasal spray: Maximum 80 sprays/day Patch: One patch/day for 8 weeks	Gum: 1 to 2 pieces/hour (2 mg/piece) Inhaler: 6 cartridges/day Lozenge: One lozenge every 1 to 2 hours Nasal spray: 1 spray in each nostril once or twice per hour Patch: One patch/day	Oral irritation, headache, dyspepsia, nasal discomfort, cough, rhinitis	PO, intranasal, transdermal
Varenicline (Chantix)	1 mg BID up to 12 weeks	0.5 mg/day	Nausea, abnormal dreams, headache	PO

BID = two times per day, IM = intramuscular, IV = intravenous, PO = oral, SL = sublingual, SQ = subcutaneous, TID = three times per day.

Source: [19] *Table 8*

The main stages of substance use disorder treatment are crisis intervention, harm reduction, detoxification/withdrawal, active treatment, and relapse prevention. To this end, a variety of medications have been approved to assist in cessation of the use of opioids, alcohol, and nicotine (***Table 8***). Some are used for detoxification, and others are used to prevent relapse. Research has shown that medications are most effective when used in conjunction with other therapies.

In addition to these approved medications, a variety of medications are used off-label for the management of several substance use disorders, including cocaine, methamphetamine, and cannabis.

The American Society of Addiction Medicine recommends that all FDA-approved medications for the treatment of opioid use disorder should be available to all patients. Clinicians should consider the patient's preferences, past treatment history, current state of illness, and treatment setting when deciding between the use of methadone, buprenorphine, and naltrexone.

(https://www.asam.org/Quality-Science/quality/2020-national-practice-guideline. Last accessed September 28, 2021.)

Level of Evidence: Expert Opinion/Consensus Statement

CASE STUDY

Patient E, 54 years of age, presents with active opioid use disorder. He began using prescription opioids for back pain after having served in the infantry. His usage eventually resulted in his leaving military service prior to retirement, and he currently works in construction. The patient reports having relied on prescription opioids until three years ago, when he started using heroin. He buys 10 bundles per day of what is described as heroin but is most likely synthetic fentanyl. He has accidentally overdosed on two occasions, and emergency medical services used naltrexone nasal spray to revive him. He is seeking care at an intensive outpatient program for treatment.

After reviewing goals of care with the patient, the clinician identifies that he has residual chronic back pain in addition to cravings for opioids when not using. The patient is diagnosed with opioid use disorder.

Patient E states that he recently sought care for his back pain and was referred to physical therapy and advised to take nonsteroidal anti-inflammatory drugs (NSAIDs) as needed for pain management. The possibility of methadone maintenance is discussed, but the patient does not want to have to go daily for dosing and is afraid that it will impair his ability to work around heavy machinery. Safety issues are also reviewed, and nasal naltrexone is prescribed for emergency use. The patient's partner receives education on use as well.

The patient states he does not wish to take a medication, but he starts attending daily 12-step meetings and working with a drug counselor. Within five days, Patient E is able to successfully complete detoxification. However, after about six weeks he experiences a relapse. His partner administers nasal naltrexone after finding him unconscious.

When Patient E returns for follow-up, various options for medication-assisted therapy are discussed, and he decides to enroll in buprenorphine/naloxone therapy, with a goal of eventually being maintained on monthly buprenorphine injection. The clinician emphasizes the need for continued counseling and the need to understand that, like all chronic diseases, patients with opioid use disorder are subject to relapse. The patient is advised of the importance of seeking help early in the event of a relapse. The biologic basis of substance use disorder is stressed; there is no judgement or shame.

Patient E does well on buprenorphine/naloxone therapy and is attending physical therapy for his back pain. He has continued with regular 12-step meetings and individual psychotherapy. At each follow-up appointment, the need to keep naltrexone nasal spray available for emergency use is emphasized.

CONCLUSION

In the management of patients with mental health disorders, pharmacotherapy remains a vital part of optimal treatment. Only a portion of the psychopharmacologic options available have been discussed in this course. When providing care to special populations, such as pediatric patients and patients who are or may become pregnant, clinicians should consult the latest literature.

Customer Information/Evaluation insert located between pages 48–49.

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Pancreatic Cancer

This course meets the Michigan requirement for 2 hours of continuing education in pain and pain symptom management.

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, is a licensed psychologist and researcher in the field of alcoholism and drug addiction based in Minnesota. He has written or contributed to the authorship of numerous papers on addiction and other medical disorders 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 various law firms on matters related to substance abuse, 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, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Division Planner
Jane C. Norman, RN, MSN, CNE, PhD

Division Planner Disclosure
The division planner has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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This activity was planned by and for the healthcare team, and learners will receive 10 Interprofessional Continuing Education (IPCE) credits for learning and change.

NetCE designates this continuing education activity for 9 pharmacotherapeutic/pharmacology contact hours.

AACN Synergy CERP Category A.

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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].

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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.

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].

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*

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*

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].

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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].

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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 are the most common precancerous precusor lesions associated with 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 Microenwironment

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.

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.

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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*

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).

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].

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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*

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.

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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].

EVIDENCE-BASED PRACTICE RECOMMENDATION

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].

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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

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*

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 noncurative 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)

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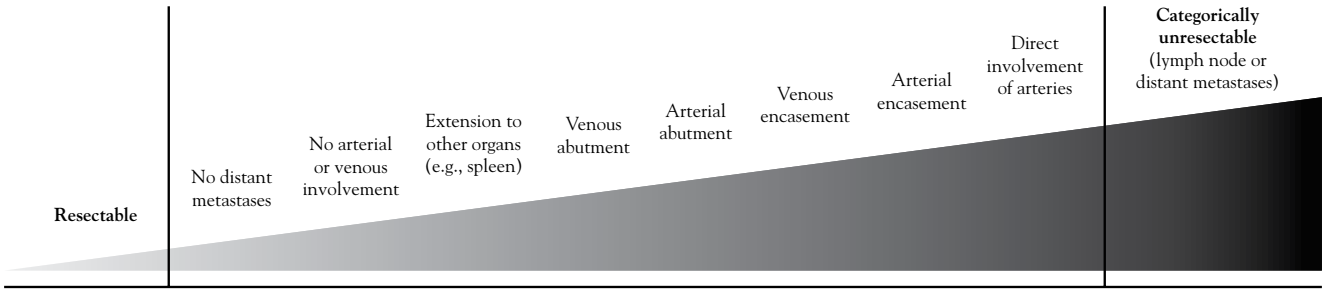
AMERICAN JOINT COMMISSION ON CANCER ANATOMIC STAGE/ PROGNOSTIC GROUPS FOR EXOCRINE PANCREATIC CANCER			
Stage	**T**	**N**	**M**
A	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1–T3	N1	M0
III	Any T	N2	M0
	T4	Any N	M0
IV	Any T	Any N	M1

Source: [93] *Table 7*

SPECTRUM OF PANCREATIC CANCER RESECTABILITY



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

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.

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

What scale is used to assess the functional status of patients with pancreatic cancer?

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].

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].

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*

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].

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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].

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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*

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].

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].

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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*

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].

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

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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.

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].

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*

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].

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*

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].

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.

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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

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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

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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.

(https://ascopubs.org/doi/10.1200/JCO.20.01364. Last accessed August 19, 2021.)

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.

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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].

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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 48–49.

Course Availability List

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PITUITARY AND ADRENAL DISORDERS

NEW!

#30830 • 15 ANCC Hours

Book By Mail – $68 • **ONLINE – $60**

Purpose: As health care becomes more complex, it is essential that the theoretical concepts of the basis of illness (pathophysiology) be well understood. The purpose of this course is to reinforce the scientific rationales for the interventions nurses perform and the decisions nurses make as patients move through the ever-changing struggle with their pituitary or adrenal illness.
Faculty: Amanda Perkins, MSN, DNP; Jane C. Norman, RN, MSN, CNE, PhD
Audience: This course is designed for nurses in all practice settings.
Additional Approval: AACN Synergy CERP Category A

PRESSURE ULCERS AND SKIN CARE

#34343 • 5 ANCC Hours

Book By Mail – $28 • **ONLINE – $20**

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 ulcers.
Additional Approval: AACN Synergy CERP Category A, CCMC

HYPERGLYCEMIA AND WOUND MANAGEMENT

#34373 • 5 ANCC Hours

Book By Mail – $28 • **ONLINE – $20**

Purpose: The impact of hyperglycemia as a comorbidity in delayed wound healing is well documented. The purpose of this course is to provide nurses with a working knowledge of preventative strategies of skin breakdown, identification of types of skin breakdown, and steps for appropriate care of wounds in patients with diabetes.
Faculty: Diane Thompson, RN, MSN, CDE, CLNC
Audience: This course is designed for nurses in all practice settings with a desire to better understand the relationship between diabetes/hyperglycemia and wound management.
Additional Approval: AACN Synergy CERP Category A, CCMC

ETHICAL DECISION MAKING

#37073 • 15 ANCC Hours

Book By Mail – $68 • **ONLINE – $60**

Purpose: The purpose of this course is to assist healthcare professionals to define the predominant ethical theories and principles used in health care, determine any legal and regulatory implications, and in collaboration with their colleagues and patients/clients, make effective decisions that determine the appropriate course
of treatment, or refusal of such, for and with those for whom they care.
Faculty: Michele Nichols, RN, BSN, MA
Audience: This course is designed for all nurses and allied healthcare professionals.
Additional Approval: AACN Synergy CERP Category B, CCMC

CARING FOR THE GERIATRIC PATIENT

#39100 • 3 ANCC Hours

Book By Mail – $23 • **ONLINE – $15**

Purpose: The purpose of this course is to provide nurses with an overview of the physical and psychosocial considerations necessary when providing care to geriatric patients.
Faculty: Alice Yick Flanagan, PhD, MSW; Allan G. Hedberg, PhD
Audience: This course is designed for nurses in a variety of practice settings who work with older patients.
Additional Approval: AACN Synergy CERP Category A, CCMC

WHAT HEALTHCARE PROFESSIONALS SHOULD KNOW ABOUT EXERCISE

UPDATE

#91723 • 5 ANCC Hours

Book By Mail – $28 • **ONLINE – $20**

Purpose: The purpose of this course is to supply the information necessary for physicians and other healthcare professionals to provide practical advice for patients beginning an exercise program.
Faculty: John J. Whyte, MD, MPH
Audience: This course is designed for physicians and will be of interest to nurses and other healthcare professionals working with adult patients who are overweight or obese and should begin an exercise program.
Additional Approval: AACN Synergy CERP Category A

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Course Availability List *(Cont'd)*

CARE OF THE PEDIATRIC TRAUMA PATIENT

#92073 • 15 ANCC Hours

Book By Mail – $68 • **ONLINE – $60**

UPDATE

Purpose: As injury remains a leading cause of mortality and morbidity among children, the purpose of this course is to allow healthcare professionals to provide timely care to pediatric trauma patients and to assist parents and caregivers in recognizing measures that prevent this type of injury.

Faculty: Susan Engman Lazear, RN, MN

Audience: This course is designed for all healthcare professionals involved in the care of pediatric patients, especially those in trauma care centers.

Additional Approval: AACN Synergy CERP Category A

AUTISM SPECTRUM DISORDER

#92203 • 5 ANCC HOURS

Book By Mail – $28 • **ONLINE – $20**

UPDATE

Purpose: The purpose of this course is to provide healthcare professionals with a basic understanding of the very complex, misunderstood, often puzzling, and sometimes disabling condition, enabling them to provide more thorough patient care, recognize symptomatology, and educate patients, families, teachers and communities about autism spectrum disorder.

Faculty: Sharon M. Griffin, RN, PhD

Audience: This course is designed for healthcare professionals in all practice settings who may be involved in the care of patients with an autism spectrum disorder.

Additional Approval: AACN Synergy CERP Category A, CCMC

THE CORONAVIRUS DISEASE (COVID-19) PANDEMIC

#94150 • 2 ANCC Hours

Book By Mail – $8 • **ONLINE – FREE**

UPDATE

Purpose: The purpose of this course is to provide physicians, nurses, and other healthcare professionals an overview of the 2019–2020 global outbreak of novel human coronavirus (SARS-CoV-2) infection, including background epidemiology, clinical features, mode of transmission, epidemic potential, and the clinical and public health measures recommended to limit the spread of infection and control the outbreak.

Faculty: John M. Leonard, MD

Audience: This course is designed for physicians, nurses, and other healthcare professionals who may identify or educate patients regarding coronavirus infection.

Additional Approval: AACN Synergy CERP Category A, CCMC

PNEUMONIA

#94673 • 10 ANCC Hours

Book By Mail – $48 • **ONLINE – $40**

UPDATE

Purpose: The purpose of this course is to provide physicians, nurses, and other healthcare professionals who manage the care of patients with pneumonia a foundation for effective management strategies in order to improve outcomes and foster an interprofessional collaborative practice consistent with published guidelines.

Faculty: Carol Whelan, APRN; Lori L. Alexander, MTPW, ELS, MWC

Audience: This course is designed for all physicians, physician assistants, and nurses, especially those working in the emergency department, outpatient settings, pediatrics, nursing homes, and intensive care units.

Additional Approval: AACN Synergy CERP Category A, CCMC

RESPONSIBLE AND EFFECTIVE OPIOID PRESCRIBING

#95151 • 3 ANCC Hours

Book By Mail – $23 • **ONLINE – $15**

Opioid/ Controlled Substance & Pain Mgmt

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

Audience: This course is designed for all physicians, osteopaths, physician assistants, pharmacy professionals, and nurses who may alter prescribing practices or intervene to prevent drug diversion and inappropriate opioid use.

Additional Approval: AACN Synergy CERP Category A, CCMC

Special Approvals: This course meets the Michigan APRN requirement for opioids and controlled substance awareness education.

DIABETES PHARMACOLOGY

#95323 • 10 ANCC Hours

Book By Mail – $48 • **ONLINE – $40**

UPDATE

Purpose: The purpose of this course is to meet the needs of healthcare professionals seeking a better understanding of the actions, dosages, onset of action, and adverse effects of diabetes medications in order to provide optimal care to their patient population.

Faculty: Diane Thompson, RN, MSN, CDE, CLNC

Audience: This course is designed for pharmacy professionals and nurses in any practice setting with a desire to familiarize themselves with the medications used in the treatment of type 2 diabetes.

Additional Approval: AACN Synergy CERP Category A, CCMC

Prices are subject to change.
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Course Availability List *(Cont'd)*

ALZHEIMER DISEASE
#96153 • 15 ANCC Hours

Book By Mail – $68 • **ONLINE – $60**

Purpose: In order to increase and maintain a reasonable quality of life for patients with Alzheimer disease throughout the course of the disease, caregivers must have a thorough knowledge and understanding of the disease. The purpose of this course is to provide clinicians with the skills to care for patients with Alzheimer disease in any setting as part of the interdisciplinary team.
Faculty: Joan Needham, MSEd, RNC
Audience: This course is designed for clinicians who come in contact with patients with Alzheimer disease in hospitals, long-term care facilities, home health care, and the office.
Additional Approval: AACN Synergy CERP Category A, CCMC

ANXIETY DISORDERS
#96181 • 15 ANCC Hours

Book By Mail – $68 • **ONLINE – $60**

Purpose: The purpose of this course is to provide healthcare professionals with the knowledge and skills necessary to appropriately identify and treat patients with anxiety disorders, addressing knowledge gaps, enhancing clinical skills, and improving patient outcomes.
Faculty: Mark Rose, BS, MA
Audience: This course is designed for health and mental health providers involved in the identification, treatment, and care of patients with anxiety disorder.
Additional Approval: AACN Synergy CERP Category A, CCMC

HUMAN TRAFFICKING AND EXPLOITATION
#96312 • 5 ANCC Hours

MI Mandate

Book By Mail – $28 • **ONLINE – $20**

Purpose: As human trafficking becomes an increasingly more common problem in the United States, healthcare and mental health professionals will require knowledge of human trafficking patterns, the health and mental health needs of human trafficking victims, and successful interventions for victims. The purpose of this course is to increase the level of awareness and knowledge about human trafficking and exploitation so health and mental health professionals can identify and intervene in cases of exploitation.
Faculty: Alice Yick Flanagan, PhD, MSW
Audience: This course is designed for physicians, nurses, social workers, pharmacy professionals, therapists, mental health counselors, and other members of the interdisciplinary team who may intervene in suspected cases of human trafficking and/or exploitation.
Additional Approval: AACN Synergy CERP Category B, CCMC
Special Approvals: This course fulfills the Michigan requirement for training in identifying victims of human trafficking.

SUICIDE ASSESSMENT AND PREVENTION
#96441 • 6 ANCC Hours

Book By Mail – $32 • **ONLINE – $24**

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
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

HERBAL MEDICATIONS: AN EVIDENCE-BASED REVIEW
#98393 • 10 ANCC Hours

Book By Mail – $48 • **ONLINE – $40**

Purpose: Considering the pharmacological interactions between herbal medications (HMs) and conventional medications, it is paramount to increase the awareness and knowledge of healthcare professionals about HMs. The purpose of this course is to increase healthcare professionals' awareness of the potential risks and benefits of HMs from an evidence-based perspective and promote the planned inclusion of HM use in patients' medical history. This course should allow healthcare professionals to discuss HMs in a knowledgeable and succinct manner with patients and colleagues.
Faculty: A. José Lança, MD, PhD
Audience: This course is primarily designed for physicians, pharmacists, and nurses. However, considering the widespread availability and increased use of herbal medications, other healthcare professionals, including social workers and clinical therapists, will also benefit from this course.
Additional Approval: AACN Synergy CERP Category A, CCMC

AGING AND LONG-TERM CARE
#99353 • 3 ANCC Hours

Book By Mail – $23 • **ONLINE – $15**

Purpose: The purpose of this course is to provide the tools necessary for social workers, counselors, mental health professionals, and allied health professionals to successfully assess and care for older adults, an increasingly large portion of the U.S. population.
Faculty: Alice Yick Flanagan, PhD, MSW
Audience: This course is designed for nurses, social workers, counselors, mental health professionals, and allied health professionals involved in the care of older adults.
Additional Approval: AACN Synergy CERP Category B, CCMC

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	97000	Implicit Bias in Health Care / 3 Contact Hours	$15
	95230	Psychopharmacology / 10 Contact Hours	$40
	90240	Pancreatic Cancer / 10 Contact Hours	$40

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2. _____ Hours	2. _____ Hours	2. _____ Hours	2. _____ Hours
3. ☐ Yes ☐ No	3. ☐ Yes ☐ No	3. ☐ Yes ☐ No	3. ☐ Yes ☐ No
4. ☐ Yes ☐ No	4. ☐ Yes ☐ No	4. ☐ Yes ☐ No	4. ☐ Yes ☐ No
5. ☐ Yes ☐ No	5. ☐ Yes ☐ No	5. ☐ Yes ☐ No	5. ☐ Yes ☐ No
6. ☐ Yes ☐ No	6. ☐ Yes ☐ No	6. ☐ Yes ☐ No	6. ☐ Yes ☐ No
7. ☐ Yes ☐ No	7. ☐ Yes ☐ No	7. ☐ Yes ☐ No	7. ☐ Yes ☐ No
8. ☐ Yes ☐ No	8. ☐ Yes ☐ No	8. ☐ Yes ☐ No	8. ☐ Yes ☐ No
9. ☐ Yes ☐ No	9. ☐ Yes ☐ No	9. ☐ Yes ☐ No	9. ☐ Yes ☐ No
10. ☐ Yes ☐ No	10. ☐ Yes ☐ No	10. ☐ Yes ☐ No	10. ☐ Yes ☐ No
11. ☐ Yes ☐ No	11. ☐ Yes ☐ No	11. ☐ Yes ☐ No	11. ☐ Yes ☐ No
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13. ☐ Yes ☐ No	13. ☐ Yes ☐ No	13. ☐ Yes ☐ No	13. ☐ Yes ☐ No

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#95230 Psychopharmacology — 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? _____

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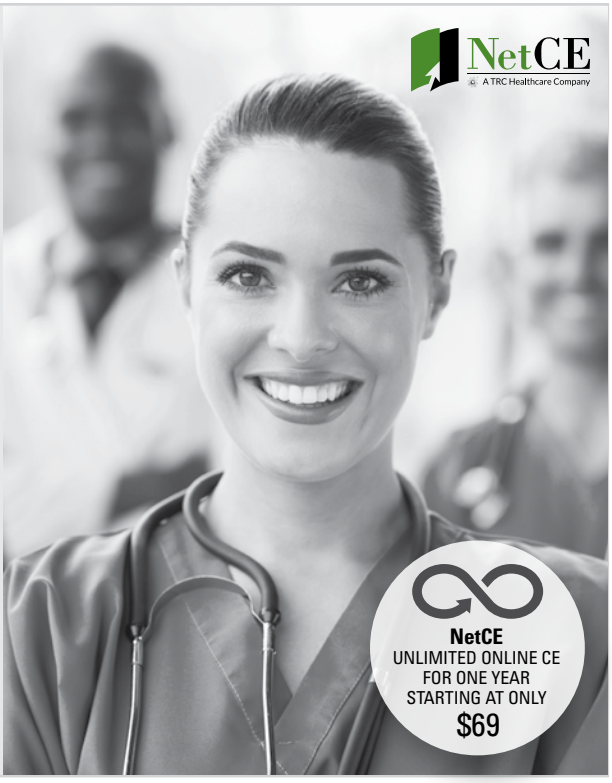

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