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# Alzheimer Disease and Dementias: Early Detection and Care Planning

**Audience**

This course is designed for nursing professionals who are involved in the care of patients who have or may develop dementia.

**Course Objective**

The purpose of this course is to provide healthcare professionals with a clear understanding of Alzheimer disease and other dementias, including early signs, stages, and progression, in order to support effective early diagnosis, care planning, and management that improves patients' quality of life.

**Learning Objectives**

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

1. Identify the warning signs and symptoms of Alzheimer disease and other forms of dementia.
2. Recognize the importance of early detection and diagnosis of dementia.
3. Recognize a variety of tools to assess a patient's cognition.
4. Identify cognitive assessment and care planning billing codes.
5. Identify current treatments available for patients with dementia.
6. Apply appropriate communication techniques for discussing memory concerns with patients and their caregivers.

**Faculty**

**Candace Pierce, DNP, RN, CNE, COI**, is a nurse leader committed to ensuring nurses are well-prepared and offered abundant opportunities and resources to enhance their skills acquisition and confidence at the bedside. With 15 years in nursing, she has worked at the bedside, in management, and in nursing education. She has demonstrated expertise and scholarship in innovation and design thinking in health care and education, and collaborative efforts within and outside of healthcare. Scholarship endeavors include funded grants, publications, and presentations. As a leader, Dr. Pierce strives to empower others to create and deploy ideas and embrace their professional roles as leaders, change agents, and problem solvers. In her position as the lead nurse planner for Elite, she works as a project engineer with subject matter experts to develop evidence-based best practices in continuing education for nurses and other healthcare professionals.

**Faculty Disclosure**

Contributing faculty, Candace Pierce, DNP, RN, CNE, COI, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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## INTRODUCTION

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### *What is the most common type of dementia?*

Dementia, including Alzheimer disease, is a significant and growing concern globally, particularly among the elderly population. According to the World Health Organization (WHO), more than 55 million people worldwide are living with dementia, and this number is expected to rise to 88 million by 2030 and 139 million by 2050 [1]. Alzheimer disease is the most common form of dementia, accounting for 60% to 70% of cases. In the United States alone, the Alzheimer's Association reports that more than 6 million Americans older than 65 years of age are living with Alzheimer disease, a number projected to reach nearly 13 million by 2050 [2; 3]. This condition not only leads to a progressive decline in cognitive function, severely impacting memory, thinking, and social abilities, but also places a substantial emotional, physical, and financial burden on families and caregivers. Early detection and diagnosis are crucial for managing symptoms, planning for the future, and improving the quality of life for those affected. Understanding the different types of dementia, their symptoms, and the importance of early intervention is essential for providing compassionate and effective care to those living with these conditions.

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## OVERVIEW OF DEMENTIA

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Dementia is a term for a decline in cognitive function severe enough to interfere with daily life and activities [4; 5]. It includes symptoms affecting memory, thinking, and social abilities, making everyday tasks challenging. Dementia is a syndrome resulting from various conditions, such as Alzheimer disease, vascular dementia, Lewy body dementia, and frontotemporal dementia. Each type has unique symptoms and progression, but common signs include memory loss, difficulty with problem-solving, impaired judgment, and changes in behavior and personality (*Table 1*).

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## IMPACT ON PATIENTS AND FAMILIES

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### *What is the primary benefit of early detection of Alzheimer disease?*

The impact of Alzheimer disease and related dementias (ADRDs) extends beyond the individual, profoundly affecting families and caregivers emotionally, physically, and financially. Patients with dementia experience a progressive decline in cognitive function, leading to increased dependency on caregivers for daily activities. This results in significant stress, burnout, and a need for support among caregivers [4].

The economic burden of dementia is substantial. In the United States, the total cost of care for individuals with Alzheimer disease and other dementias was estimated at \$321 billion in 2022, with projections reaching nearly \$1 trillion by 2050 due to rising prevalence and healthcare costs. These costs include medical care, long-term care, and the value of unpaid caregiving by family members [4].

Early detection and diagnosis of dementia are crucial for managing symptoms, planning for the future, and improving the quality of life for those affected. Understanding the prevalence and impact of dementia is essential for developing effective strategies and support systems to address this growing public health challenge.

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## ALZHEIMER DISEASE

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Alzheimer disease is a progressive neurodegenerative disorder affecting older adults, leading to significant cognitive decline that interferes with daily life. It is the most common form of dementia, accounting for 60% to 70% of cases [1]. The disease is marked by amyloid plaques and tau tangles in the brain, disrupting neuronal communication and causing cell death. Early symptoms include memory loss, difficulty in planning and problem-solving, and challenges with language and spatial awareness. As it progresses, individuals may experience severe memory impairment, confusion, mood changes, and difficulty with basic activities [12].

The exact cause of Alzheimer disease is not fully understood but is believed to involve genetic, environmental, and lifestyle factors. Major risk factors include age (primarily affecting those older than 65 years of age) and gender (more common in women). Other risks include family history, genetic mutations, and conditions like cardiovascular disease and diabetes. There is no cure, but treatments can temporarily slow symptom progression and improve quality of life. Ongoing research aims to uncover the disease's mechanisms and develop more effective therapies [4; 10].

### THE LONG PRECLINICAL PHASE OF ALZHEIMER DISEASE

Research indicates that Alzheimer disease can begin 20 years or more before clinical symptoms appear [12; 13]. During this preclinical phase, amyloid-beta plaques and tau tangles accumulate in the brain, disrupting neuronal function and leading to gradual brain cell death.

This period is marked by subtle brain changes that are not yet noticeable. Advanced imaging techniques and biomarkers, like cerebrospinal fluid analysis, can detect these early changes, offering insights into disease progression [2]. Identifying individuals in this stage is crucial for early intervention and developing treatments to slow or halt the disease before significant cognitive impairment occurs.

TYPES OF DEMENTIA		
Disease	Symptoms	Attributes/Causation
Parkinson disease	Poor executive function Trouble walking, unstable gait Impaired responsiveness to visual cues Speech impairment Impaired affect/modified facial expression Decreased eye blinking Depression Confusion Insomnia Rigidity/freezing, tremor Alzheimer disease traits (memory loss, confusion, and language changes)	Basal ganglia cells die, causing dopamine levels to drop Progressive, chronic disease Personalized treatments for symptom relief Exercise can improve symptoms and may protect the brain No cure
Frontotemporal dementia (FTD)	Frontal lobe brain cell damage due to nerve damage Diagnosis confirmed postmortem Drastic change in behavior and personality Aggression Loss of speech Loss of decision-making ability Loses sense of self-awareness Patient will become completely dependent	Frontal lobe controls language and personality Also known as Pick disease No cure
Lewy body dementia (LBD)	Progressive dementia Affects ability to think, reason, and process information Impaired movement, mood, and behavior Parkinsonian-like rigidity Hallucinations, paranoia	1.4 million people living with this disease Due to unusual deposits of alpha-synuclein protein on brain Initial diagnosis may be mental/psychological health No cure
Vascular dementia	Problems with reasoning Impacted judgement, memory, and other thought processes Symptoms vary by location of actual constriction	Caused by constriction or breakdown of blood vessels in and around the brain Can be the result of a stroke(s) Lifestyle factors (diet, lack of movement, smoking) contribute to disease progression Disease can be allayed by exercise, diet, avoiding alcohol and smoking
Chronic traumatic encephalopathy (CTE)	Memory loss, confusion Mood disorder, personality changes, rage Can present in mid-life Person becomes erratic and unpredictable	Originally referred to as punch drunk syndrome Caused by extensive hits to the head Brain has tau protein like Alzheimer disease, but presents uniquely in CTE Some symptoms can be addressed with medication Diagnosed postmortem No cure
Atypical Alzheimer disease	Amnesic problems Unusually early symptoms impacting executive and motor functioning	Frontal variant of Alzheimer disease Posterior cortical atrophy
Mixed dementia	Similar to Alzheimer disease or other form of dementia Varied symptoms suggest multiple forms of dementia	Most often diagnosed as Alzheimer disease Co-existing pathology, such as blood clots or vascular disease, found postmortem Impacted by relationship between cognitive function and underlying brain abnormalities

Table 1 continues on next page.

TYPES OF DEMENTIA (Continued)		
Disease	Symptoms	Attributes/Causation
Corticobasal syndrome (CBS)	Asymmetric limb rigidity, dystonia, muscle jerks (myoclonus), difficulty with motor planning (apraxia) Progressive difficulty with language (aphasia), executive functioning, and visuospatial impairments Changes in personality, irritability, and apathy	Associated with abnormal tau protein accumulation in the brain, leading to neuronal degeneration Often linked to corticobasal degeneration (CBD), a rare neurodegenerative disease
Creutzfeldt-Jakob disease (CJD)	Rapid cognitive decline with memory loss, confusion, and personality changes Muscle jerks (myoclonus), loss of coordination (ataxia), visual disturbances, and speech abnormalities Anxiety, depression, and psychosis	Caused by prions, which are misfolded proteins that lead to brain damage Can be sporadic, inherited, or acquired through exposure to infected tissue
HIV-associated neurocognitive disorder (HAND)	Memory loss, difficulty concentrating, and executive dysfunction Slowed movements, clumsiness, and coordination problems Apathy, depression, and social withdrawal	Caused by the direct effects of HIV on the central nervous system, leading to inflammation and neuronal damage
Huntington disease	Involuntary jerking movements (chorea), dystonia, slowed movements (bradykinesia) Progressive decline in executive function, memory, and attention Depression, irritability, anxiety, and impulsivity	A genetic disorder caused by a mutation in the HTT gene, leading to the production of an abnormal huntingtin protein that causes neuronal death
Normal pressure hydrocephalus (NPH)	Difficulty walking, shuffling gait, and balance problems Memory loss, confusion, and difficulty with attention and decision-making Urinary incontinence and urgency	Caused by an abnormal buildup of cerebrospinal fluid (CSF) in the brain's ventricles, leading to increased pressure and damage to brain tissues
Progressive supranuclear palsy (PSP)	Difficulty with balance and walking, frequent falls, and stiffness Difficulty moving the eyes, particularly in the vertical direction Executive dysfunction, slowed thinking, and memory problems Apathy, depression, and personality changes	Caused by the accumulation of tau protein in the brain, leading to the degeneration of specific brain regions, particularly those involved in movement and cognitive function

Source: [6; 7; 8; 9; 10; 11]

Table 1

Recognizing that Alzheimer disease starts decades before symptoms manifest highlights the importance of early detection and monitoring. It also emphasizes the need for ongoing research to develop preventive strategies and treatments targeting the disease's earliest stages. By focusing on the preclinical phase, healthcare providers can better manage the eventual onset of symptoms, improving outcomes for patients and their families.

### STAGES OF ALZHEIMER DISEASE

Alzheimer disease progresses through stages marked by increasing cognitive and functional decline. The Reisberg Scale, or Global Deterioration Scale (GDS), divides this progression into seven stages, grouped into early, middle, and late stages:

- Early stages (1–3): Mild cognitive changes that may not be immediately recognized as Alzheimer disease

AGE-RELATED VERSUS POTENTIAL ADRD DIFFERENTIALS	
Normal Age-Related Memory Issues	Potential ADRD
Occasionally making a bad decision	Making poor judgements and decisions occurs frequently
Misplacing or losing things occasionally	Frequently losing items and being unable to locate them
Accidentally missing a bill payment	Getting the electricity or water shut off for lack of payment over a period of time
Occasionally lacking the ability to grasp a specific word	Difficulties following or participating in a conversation
Momentarily forgetting the day of the week	Having an inability to track time; being unable to discern day or week or season
Source: [14]	

Table 2

- Middle stages (4–5): More pronounced cognitive decline and increased dependency on caregivers
- Late stages (6–7): Severe cognitive and physical impairment, requiring comprehensive care and support

Recognizing these stages aids in planning appropriate interventions and support for individuals with Alzheimer disease and their caregivers.

**Early Stage (Stages 1–3)**

**Stage 1: No Cognitive Decline**

Description: No noticeable symptoms of cognitive impairment. The individual functions normally, with no memory problems or other signs of dementia.

Fit into early stage: This stage represents normal cognitive function without any detectable signs of Alzheimer disease.

**Stage 2: Very Mild Cognitive Decline**

Description: Minor memory lapses, such as forgetting familiar words or the location of everyday objects. These lapses are not evident to friends, family, or medical professionals.

Fit into early stage: This stage is often considered normal age-related memory decline and may not be recognized as Alzheimer disease.

**Stage 3: Mild Cognitive Decline**

Description: Noticeable difficulties in memory and concentration. Common symptoms include losing valuable objects, trouble remembering names, and difficulty performing tasks in social or work settings. Friends and family may notice these changes.

Fit into early stage: This stage marks the beginning of noticeable cognitive impairment, often referred to as mild cognitive impairment. It is a critical period for early diagnosis and intervention.

**Middle Stage (Stages 4–5)**

**Stage 4: Moderate Cognitive Decline (Mild or Early-Stage Alzheimer Disease)**

Description: Clear-cut symptoms of Alzheimer disease become apparent. Individuals may have difficulty with complex tasks such as managing finances, planning events, and remembering recent events. They may also become moody or withdrawn, especially in socially or mentally challenging situations.

Fit into middle stage: This stage is characterized by a decline in cognitive abilities that affects daily life. It is often when a formal diagnosis of Alzheimer disease is made.

**Stage 5: Moderately Severe Cognitive Decline (Moderate or Mid-Stage Alzheimer Disease)**

Description: Significant gaps in memory and cognitive function. Individuals may need help with daily activities such as dressing and grooming. They may forget important details like their address or phone number and may become confused about the date or time.

Fit into middle stage: This stage involves more severe cognitive decline and increased dependency on caregivers for daily activities.

**Late Stage (Stages 6–7)**

**Stage 6: Severe Cognitive Decline (Moderately Severe or Mid-Stage Alzheimer)**

Description: Memory continues to worsen, and personality changes may occur. Individuals may lose awareness of their surroundings and recent experiences. They often need extensive help with daily activities and may experience changes in sleep patterns, increased wandering, and difficulty recognizing loved ones.

Fit into late stage: This stage marks a significant decline in cognitive and functional abilities, requiring substantial caregiving support.



CONDITIONS AND EVENTS THAT MAY MIMIC DEMENTIA SYMPTOMS	
Condition/Event	Symptom(s)
Polypharmacy	Confusion, memory problems, cognitive impairment
Respiratory infection	Hypoxia (low oxygen levels), causing confusion and cognitive decline
Urinary tract infection	Acute confusion, agitation, hallucinations
Sleep disorder	Daytime sleepiness, memory problems, decreased cognitive function
Dehydration	Confusion, dizziness, cognitive impairment
Normal pressure hydrocephalus	Walking difficulties, urinary incontinence, cognitive decline
Metabolic/endocrine imbalance	Impaired cognitive function (particularly with thyroid disorders, diabetes)
Nutritional deficiencies (e.g., vitamin B12)	Memory loss, cognitive decline
Alcohol use	Cognitive impairment, memory problems
Subdural hematoma	Steady decline in overall mental function
Poisoning/toxic exposure (heavy metals, pesticides)	Cognitive impairment
Anoxia	Cognitive impairment, somnolence
<i>Source: Compiled by Author</i>	

Table 3

### Stage 7: Very Severe Cognitive Decline (Severe or Late-Stage Alzheimer)

Description: Individuals lose the ability to respond to their environment, carry on a conversation, and eventually control movement. They may need help with all daily activities, including eating and using the bathroom. Reflexes become abnormal, and muscles grow rigid. Swallowing can become impaired.

Fit into late stage: This final stage of Alzheimer disease involves profound cognitive and physical decline, with individuals requiring around-the-clock care.

### EARLY WARNING SIGNS AND SYMPTOMS

Early warning signs and symptoms of Alzheimer disease often manifest subtly and can be easily mistaken for normal aging (*Table 2*). One of the most common early signs is memory loss, particularly difficulty remembering recently learned information or important dates and events [2]. Individuals may also experience challenges in planning or solving problems, such as difficulty following a familiar recipe or managing monthly bills. Confusion with time or place, such as losing track of dates, seasons, and the passage of time, is another early indicator. Additionally, people with early Alzheimer disease may have trouble understanding visual images and spatial relationships, leading to difficulties with reading, driving, judging distance, and determining color or contrast [12]. Other symptoms include new problems with words in speaking or writing, misplacing things and losing the ability to retrace steps, decreased or poor judgment, withdrawal from work or social activities, and changes in mood and personality, such as increased confusion, suspicion, depression, or anxiety [10].

Recognizing these early signs is crucial for timely diagnosis and intervention, which can help manage symptoms and improve the quality of life for those affected.

ADRDs can also present with symptoms like those of medical conditions that are potentially reversible. Recognizing these conditions is crucial, as addressing them can significantly improve cognitive function and quality of life. *Table 3* identifies some common conditions that can mimic dementia symptoms.

Addressing these conditions through appropriate medical intervention can lead to significant improvement or complete resolution of symptoms that mimic dementia, highlighting the importance of thorough medical evaluation in individuals presenting with cognitive decline.

### IMPORTANCE OF EARLY DETECTION AND DIAGNOSIS

Early detection of Alzheimer disease and other dementias offers significant benefits for patients and their families. It can improve quality of life by allowing access to treatments that slow symptom progression, helping individuals maintain independence longer [7]. Early diagnosis also enables better symptom management through personalized care plans that address cognitive, behavioral, and physical health needs [12].

Additionally, early detection allows for future planning, helping patients and families make informed decisions about legal, financial, and care arrangements, reducing stress and ensuring the patient's wishes are respected [10]. It also provides opportunities for participation in clinical trials and research, contributing to advancements in treatment.


TESTS/EXAMINATIONS TYPICALLY USED TO DIAGNOSE ALZHEIMER DISEASE	
Test/Examination	Assessment
Montreal Cognitive Assessment (MoCA)	Evaluates short-term memory, visuospatial abilities, attention/concentration/memory, executive function, language, and orientation to time and place
Mini-Mental State Examination (MMSE)	Short test that assesses executive function, information registration, recall, language, ability to follow simple commands, and orientation to time and place
Bloodwork	Complete blood count (CBC) Liver function Glucose Thyroid function HIV Electrolytes Folate test Vitamin B12 concentration
CT scan	Evaluate the severity of brain degeneration
Magnetic resonance imaging (MRI)	Deep insight into brain looking for tumors, nerve damage, and unusual markings
Electroencephalogram (EEG)	Measure and evaluate brain wave activity
Positron emission tomography (PET)	Identify Alzheimer disease amyloid proteins
Source: [2]	

Table 4

## DIAGNOSTIC PROCESS

The diagnostic process for dementia involves several steps to ensure an accurate and comprehensive assessment. Initially, healthcare providers conduct a thorough medical history review and physical examination to rule out other potential causes of cognitive decline. This is followed by cognitive and neuropsychological testing to evaluate memory, problem-solving abilities, language skills, and other cognitive functions [12]. Imaging studies, such as MRI or CT scans, are often used to detect brain changes associated with dementia, while laboratory tests can help identify underlying conditions that may contribute to cognitive impairment. **Table 4** provides more details on tests and examinations that may be used to diagnose Alzheimer disease.

Healthcare providers play a crucial role in early detection of dementia. Primary care providers, neurologists, and geriatric specialists often notice early signs during routine check-ups or when patients present with memory concerns. They initiate the diagnostic process, coordinate care, and refer patients to specialists as needed. Additionally, they educate and support patients and families, helping them understand the diagnosis and navigate dementia care complexities [7].



The American Psychological Association asserts that an interdisciplinary team is most likely to provide all the essential information necessary to make an accurate diagnosis of dementia and develop a comprehensive treatment plan.

(<https://www.apa.org/practice/guidelines/guidelines-dementia-age-related-cognitive-change.pdf>. Last accessed August 21, 2024.)

**Level of Evidence:** Expert Opinion/Consensus Statement

## ASSESSING COGNITION

### Assessment Tools

*Which cognitive assessment tool is commonly used for a quick screening in a primary care setting?*

Cognitive assessment tools are crucial for diagnosing and monitoring Alzheimer disease and other dementias. They evaluate cognitive domains like memory, attention, language, and executive function. Common tools include the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and clock drawing test (CDT) [15; 16; 17; 18].

COMMONLY USED DIAGNOSTIC CODES	
Code	Description
G31.09	Frontotemporal Dementia
G31.83	Dementia with Lewy Bodies
G31.84	Mild Cognitive Impairment
G30.0	Alzheimer's Disease with Early Onset
G30.1	Alzheimer's Disease with Late Onset
G30.9	Alzheimer's Disease Unspecified
F03.90	Unspecified Dementia without Behavioral Disturbance
F03.91	Unspecified Dementia with Behavioral Disturbance
F01.50	Vascular Dementia without Behavioral Disturbances
F01.51	Vascular Dementia with Behavioral Disturbances
F02.80	Dementia in Other Diseases Classified Elsewhere with Behavioral Disturbances
F02.81	Dementia in Other Diseases Classified Elsewhere with Behavioral Disturbances
F03.91	Unspecified Dementia with Behavioral Disturbances

Source: Compiled by Author Table 5

The MMSE assesses orientation, registration, attention, calculation, recall, language, and simple commands, scoring out of 30 points. Scores of 24–30 are normal, 18–23 indicates mild impairment, and 0–17 suggests severe impairment. The MoCA provides a comprehensive assessment, including visuospatial abilities, naming, memory, attention, language, abstraction, and orientation, with scores less than 26 indicating impairment. The CDT evaluates executive function and visuospatial abilities by having patients draw a clock showing a specific time [15; 16; 17; 18].

Administering these tools requires a standardized approach for accuracy. The MMSE and MoCA involve guided tasks and scoring, while the CDT involves drawing a clock. Scores are compared with normative data, considering age, education, and cultural background [15; 16; 17; 18].

Choosing the right tool depends on the patient's clinical presentation and the cognitive domains needing assessment. Other factors to consider include the patient's language proficiency, cultural background, and any sensory or motor impairments that may affect their performance on the tests. Healthcare providers should also consider the psychometric properties of the tools, such as their sensitivity, specificity, and reliability, to ensure accurate and meaningful results. The MMSE is good for quick screenings, the MoCA for comprehensive evaluations, and the CDT for executive function and visuospatial skills. Multiple tools can enhance diagnostic accuracy, with the MoCA being particularly sensitive for early impairment detection [15; 18].

## COGNITIVE ASSESSMENT BILLING

### *What is the purpose of CPT Code 99483?*

Billing for cognitive assessment and care planning is essential for ensuring that healthcare providers are reimbursed for the time and resources spent on these critical services. The Centers for Medicare & Medicaid Services (CMS) have established specific billing codes for cognitive assessment and care planning services. These codes allow healthcare providers to bill for the time spent on comprehensive cognitive assessments and care planning for patients with cognitive impairment, including Alzheimer disease and other dementias [4]. The primary codes include [19]:

- CPT code 99483: Used for a comprehensive cognitive assessment and care planning for patients with cognitive impairment, including Alzheimer disease and other dementias. It covers services such as evaluating cognition, functional status, medication review, and the development of a care plan. Clinicians allowed to bill under this code include physicians, physician assistants, nurse practitioners, clinical nurse specialists, and certified nurse midwives. This code can be used once per 180 days (about every 6 months).
- CPT code 99484: Used for standardized cognitive performance testing, which includes the administration and scoring of tests to assess cognitive function

The code HCPCS code G0505 was previously used for cognitive and functional assessment and care planning for patients with cognitive impairment, including Alzheimer disease and other dementias. It has been replaced by CPT Code 99483 [20]. **Table 5** lists other diagnostic codes commonly used in the care of cognitive impairment or dementia.

ALZHEIMER DISEASE STAGE AND FAMILY ISSUES		
Disease Stage	Issues/Concerns of Family	Steps to Address
Early (Stages 1-3)	Accept and address an uncertain future. Identify potential areas of internal family conflict. Recognize that Alzheimer disease can often unveil past conflict.	Form a cohesive family alliance. Seek professional guidance (elder law attorneys, financial planners, social workers). Identify long-term care needs and desires for the person with Alzheimer disease. Establish an honest, open, and supportive communication method. Acknowledge collective grief and loss as the loved one declines.
Middle (Stages 4-5)	Caregiving needs become more intense to include financial, home safety, and some life management.	Family members/caregivers may feel trapped, leading to new or worsened conflicts. There may be a sense of lost freedom due to disease-related limitations. It can be hard to separate the person from the illness, necessitating additional support (e.g., respite care). Managing disease symptoms (wandering, mood swings, sleep changes) can be challenging. Balancing work, caregiving, and personal life may seem impossible as needs increase. Without prior planning, families face tough decisions about living arrangements, finances, and external support. Family members may experience grief, health issues, anger, denial, and exhaustion.
Late (Stages 6-7)	Patient will need full-time support for all activities of daily living. Family members may find themselves dealing with effects of long-term caregiving (e.g., financial and health challenges, inability to work, poor self-care).	Family cohesion may suffer due to concerns about providing safe, proper care (e.g., transferring, feeding, supervision). Long-term planning can ensure the person receives hospice care or allows the family to decide. The person is vulnerable to normal age-related health issues. Family may experience exhaustion and worry about their own well-being and the impact on their children and spouse. Long-term stress and grief can affect family relationships and cohesion, especially without planning. Family members may face physical and mental health challenges requiring additional support and lifestyle changes.
Source: [23]		Table 6

More information can be found on billing codes specific to cognitive impairment by the Alzheimer’s Association in their Cognitive Impairment Care Planning Toolkit found at [https://www.alz.org/media/Documents/Cognitive-Impairment-Care-Planning-Toolkit\\_1.pdf](https://www.alz.org/media/Documents/Cognitive-Impairment-Care-Planning-Toolkit_1.pdf).

**DOCUMENTATION**

Proper documentation is crucial for billing cognitive assessments accurately. It is also important to note that the total time spent on the assessment and care planning must meet the

minimum requirements for the chosen billing code (typically 50 minutes for CPT code 99483). When using CPT Code 99483, healthcare providers should conduct a detailed assessment and document the assessment findings to include test scores and interpretations, clinical observations, and patient and caregiver reports. The detailed assessment should include:

- Cognitive assessment using standardized tools (e.g., MMSE, Montreal Cognitive Assessment): Detailed evaluation of the patient’s cognitive function, including memory, attention, language, and executive function

- Functional assessment: Evaluation of the patient's ability to perform activities of daily living (ADLs) and instrumental activities of daily living (IADLs)
- Medication review: Comprehensive review of all medications the patient is taking, including prescription drugs, over-the-counter medications, and supplements
- Safety evaluation: Assessment of the patient's safety, including risks of falls, wandering, and other hazards
- Caregiver assessment: Evaluation of the caregiver's needs and the impact of caregiving on their health and well-being

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## CARE PLANNING

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Care planning is essential in managing Alzheimer disease and other dementias, addressing multiple aspects of the patient's health and well-being. A comprehensive care plan should outline treatment goals, medication management strategies, safety measures (e.g., fall prevention), and methods to manage behavioral symptoms. It should also include cognitive stimulation activities, social engagement recommendations, and caregiver support and education. Early advance care planning discussions are crucial to ensure the patient's wishes are respected as the disease progresses. Referrals to specialists and community resources should be included for comprehensive support.

Person-centered care is vital, involving both the patient and caregivers in the planning process [22]. Healthcare providers should use clear language when explaining assessments and treatment options, encouraging patients to express their preferences and concerns.

Caregivers should be included in discussions about care goals and management strategies, as they often play a primary role in day-to-day care. Education about the disease process, expected progression, and available resources should be provided to both patients and caregivers. The needs of the family evolve as Alzheimer disease progresses, and this should be considered at all phases of patient care (*Table 6*). The importance of advance directives should be discussed, and their completion encouraged. Regular reviews and updates of the care plan, with input from both the patient and caregiver, ensure its relevance and effectiveness as the disease progresses. Throughout the process, healthcare providers should offer opportunities for patients and caregivers to ask questions and voice concerns, fostering a collaborative approach to care management.

## COMMUNICATION TECHNIQUES

Effective communication is crucial when caring for patients who have Alzheimer disease or other dementias. Healthcare providers should use clear, simple language, speak slowly, and maintain eye contact when discussing memory concerns. It is important to approach the topic sensitively, acknowledging the patient's feelings and concerns [24]. Building trust and rapport involves active listening, showing empathy, and respecting

the patient's dignity. Providers should create a comfortable environment and allow ample time for the patient to process information and respond [22].

Engaging caregivers is equally important. Strategies include educating them about the disease, its progression, and available resources. Caregivers should be encouraged to participate in appointments and care planning discussions. Addressing caregiver concerns involves providing emotional support, offering respite care information, and connecting them with support groups. Healthcare providers should also assess caregiver stress and burnout, offering strategies for self-care and stress management [25]. By fostering open communication with both patients and caregivers, providers can ensure more comprehensive and effective care for individuals with dementia.

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## TREATMENT OPTIONS

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### *What is the primary function of cholinesterase inhibitors in the treatment of Alzheimer disease?*

Pharmacological treatments for dementia focus on managing symptoms and slowing disease progression. The main medications include cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and an N-methyl-D-aspartate (NMDA) receptor antagonist, memantine. Cholinesterase inhibitors increase acetylcholine levels, improving cognitive function and behavioral symptoms in mild-to-moderate Alzheimer disease [2]. Memantine regulates glutamate activity and is used for moderate to severe Alzheimer disease. These medications can improve cognition, mood, and daily functioning but may have side effects. Cholinesterase inhibitors can cause nausea, vomiting, diarrhea, dizziness, and sleep disturbances, while memantine may cause dizziness, headaches, and constipation [10]. Although they do not cure dementia, they can temporarily improve symptoms or slow their worsening [26].



The European Academy of Neurology suggests that the use of a combination of cholinesterase inhibitor (ChEI) plus memantine rather than ChEI alone may provide useful benefits in patients with moderate-to-severe Alzheimer disease.

(<https://onlinelibrary.wiley.com/doi/full/10.1111/ene.12707>. Last accessed August 21, 2024.)

**Level of Evidence:** Expert Opinion/Consensus Statement

In 2021, the FDA granted accelerated approval to aducanumab for the treatment of Alzheimer disease [27]. It is the first new treatment approved for Alzheimer disease since 2003 and is the first therapy that targets the fundamental pathophysiology of the disease. Approval of aducanumab was based on evidence

showing a significant reduction of beta amyloid plaque in those receiving the drug (compared with placebo) [27]. Preliminary studies have been conflicting, and the FDA's decision to grant accelerated approval to aducanumab was controversial. The manufacturer discontinued aducanumab in 2024 [29]. In 2023, the FDA granted accelerated approval to lecanemab for the treatment of Alzheimer disease [21]. Like aducanumab, lecanemab is an anti-amyloid monoclonal antibody, and the presence of amyloid beta pathology should be confirmed prior to treatment initiation. Lecanemab is an intravenous infusion given every two weeks at an infusion center, but subcutaneous delivery is being studied in trials.

Nonpharmacological treatments are essential for managing dementia and improving the quality of life for patients and caregivers. Cognitive therapies, such as cognitive stimulation, reminiscence therapy, and cognitive rehabilitation, enhance cognitive function, communication skills, and overall well-being [12]. These therapies engage patients in activities that stimulate thinking, memory, and social interaction. Lifestyle interventions, including regular physical exercise, social engagement, and a healthy diet, show promise in reducing dementia risk and slowing cognitive decline. These interventions are often combined with pharmacological treatments for a comprehensive care approach [2; 28].

#### FUTURE DIRECTION OF TREATMENT AND CARE

Emerging treatments and ongoing research offer hope for future dementia care. Current investigations include anti-amyloid and anti-tau therapies, neuroprotective agents, and personalized medicine approaches. Gene therapy and stem cell research are also being explored. Recent advancements, such as lecanemab, show promise in reducing amyloid plaques and potentially slowing cognitive decline [21].

Advancements in early detection and prevention strategies, like blood-based biomarkers and lifestyle interventions, are shaping the future of dementia care. While many treatments are still in development, they represent promising directions for more effective management and potential prevention of dementia [30].

Future dementia care emphasizes a holistic and personalized approach, integrating pharmacological and nonpharmacological interventions, leveraging technology for remote monitoring, and enhancing caregiver education and support. Advances in precision medicine and biomarker research are expected to enable earlier and more accurate diagnoses, allowing for timely intervention and better disease management. Ongoing research into genetic and environmental factors will likely lead to preventive strategies and more effective treatments, improving outcomes for individuals with dementia and their families [2].

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## CASE STUDY: MANAGING EARLY-STAGE ALZHEIMER DISEASE

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### INITIAL ASSESSMENT AND DIAGNOSIS

#### Background

Patient A, a 68-year-old retired teacher, has been experiencing memory lapses and difficulty with daily tasks over the past year. Her family has noticed that she often forgets recent conversations, misplaces items, and struggles with planning activities. Concerned about her cognitive decline, the patient's daughter, Ms. S, schedules an appointment with a neurologist specializing in dementia.

#### Initial Assessment

During the initial consultation, the physician conducts a thorough medical history review and physical examination. Patient A undergoes cognitive testing using the MMSE and the MoCA. Her MMSE score is 24/30, and her MoCA score is 22/30, indicating mild cognitive impairment. The physician also orders an MRI to rule out other potential causes of cognitive decline.

#### Diagnosis

Based on the cognitive assessment and imaging results, Patient A is diagnosed with early-stage Alzheimer disease. He explains the diagnosis to Patient A and her daughter, emphasizing the importance of early detection and intervention.

#### Discussion Questions

1. What were the early signs of Alzheimer disease that this patient exhibited?

*Answer: Patient A exhibited memory lapses, difficulty with daily tasks, forgetting recent conversations, misplacing items, and struggling with planning activities.*

2. Which cognitive assessment tools were used to evaluate Patient A's cognitive function?

*Answer: The MMSE and the MoCA were used to evaluate the patient's cognitive function.*

3. What is the significance of early detection and diagnosis in this patient's case?

*Answer: Early detection and diagnosis allowed for timely intervention, enabling Patient A to access treatments and interventions that can slow the progression of symptoms and improve her quality of life. It also provided an opportunity for her and her family to plan for the future and make informed decisions about her care.*

## CARE PLAN DEVELOPMENT AND IMPLEMENTATION

*What is the significance of involving caregivers in the care planning process for dementia patients?*

### Care Plan Development

Patient A's physician develops a comprehensive care plan, which includes pharmacological and nonpharmacological treatments. He prescribes donepezil, a cholinesterase inhibitor, to help manage her symptoms. Additionally, he recommends cognitive stimulation therapy (CST) and encourages Patient A to engage in regular physical exercise, maintain a healthy diet, and stay socially active.

### Caregiver Involvement

Patient A's daughter is actively involved in the care planning process. The physician provides education on Alzheimer disease, its progression, and available resources. He also discusses the importance of caregiver support and suggests joining a local support group for caregivers of individuals with dementia.

### Follow-Up

The physician schedules regular follow-up appointments to monitor Patient A's condition, review the effectiveness of the care plan, and make necessary adjustments. He maintains open communication with the patient and her daughter to address any concerns and provide ongoing support.

### Discussion Questions

1. How was Ms. S involved in the care planning process, and why is caregiver involvement important?

*Answer: Ms. S was actively involved in the care planning process by participating in discussions about treatment options, goals of care, and preferences for care. Caregiver involvement is important because it ensures that the care plan is tailored to the needs and preferences of both the patient and the caregiver, providing necessary support and education.*

2. What are the key components of Patient A's comprehensive care plan?

*Answer: Key components of Patient A's comprehensive care plan include medical management with donepezil, cognitive and behavioral interventions such as CST, safety measures to prevent accidents, support services for both Patient A and her daughter, and legal and financial planning.*

3. Why are regular follow-up appointments important in managing Alzheimer disease?

*Answer: Regular follow-up appointments are important to monitor the patient's condition, review the effectiveness of the care plan, make necessary adjustments, and provide ongoing support and education to the patient and caregiver.*

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## CONCLUSION

Alzheimer disease and other dementias are complex conditions that significantly impact patients and caregivers. Understanding the stages and progression of these diseases is crucial for effective planning, lifestyle changes, and safety measures. As dementia prevalence rises, ongoing research, advanced testing, and robust communication within the dementia care community are increasingly important.

Healthcare providers play a key role in this landscape. We must collaborate as a multidisciplinary team to address care gaps, ensure effective communication, and share vital information. This empowers and supports our patients with honesty and integrity. Managing dementia requires a comprehensive, community-based approach to ensure access to necessary healthcare services and support systems. Through early detection, personalized care planning, and continuous learning, we can make a meaningful difference in the lives of those affected by dementia.

Customer Information and Evaluation are located on pages 79–80.

# Falls and Fall Prevention

## Audience

This course is designed for nurses, physicians, physician assistants, and allied professionals involved in the care of patients at risk for falls.

## Course Objective

The purpose of this course is to provide healthcare professionals with the knowledge and skills necessary to intervene to reduce fall risk in their patients.

## Learning Objectives

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

1. Discuss the epidemiology of falls and fall injuries.
2. Anticipate types and settings of fall injuries and associated cost reimbursement issues.
3. Assess community-dwelling older adults and hospital inpatients for fall risks, using office-based tools (techniques) to evaluate strength and balance.
4. Recognize the importance and lend support to health system efforts to implement an effective fall prevention program.

## Faculty

**Mary Franks, MSN, APRN, FNP-C**, is a board-certified Family Nurse Practitioner and NetCE Nurse Planner. She works as a Nurse Division Planner for NetCE and a per diem nurse practitioner in urgent care in Central Illinois. Mary graduated with her Associate's degree in nursing from Carl Sandburg College, her BSN from OSF Saint Francis Medical Center College of Nursing in 2013, and her MSN with a focus on nursing education from Chamberlain University in 2017. She received a second master's degree in nursing as a Family Nurse Practitioner from Chamberlain University in 2019. She is an adjunct faculty member for a local university in Central Illinois in the MSN FNP program. Her previous nursing experience includes emergency/trauma nursing, critical care nursing, surgery, pediatrics, and urgent care. As a nurse practitioner, she has practiced as a primary care provider for long-term care facilities and school-based health services. She enjoys caring for minor illnesses and injuries, prevention of disease processes, health, and wellness. In her spare time, she stays busy with her

two children and husband, coaching baseball, staying active with her own personal fitness journey, and cooking. She is a member of the American Association of Nurse Practitioners and the Illinois Society of Advanced Practice Nursing, for which she is a member of the bylaws committee.

**John M. Leonard, MD**, Professor of Medicine Emeritus, Vanderbilt University School of Medicine, completed his postgraduate clinical training at the Yale and Vanderbilt University Medical Centers before joining the Vanderbilt faculty in 1974. He is a clinician-educator and for many years served as director of residency training and student educational programs for the Vanderbilt University Department of Medicine. Over a career span of 40 years, Dr. Leonard conducted an active practice of general internal medicine and an inpatient consulting practice of infectious diseases.

## Faculty Disclosure

Contributing faculty, Mary Franks, MSN, APRN, FNP-C, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Contributing faculty, John M. Leonard, MD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

## Division Planner

Sharon Cannon, RN, EdD, ANEF

## Senior Director of Development and Academic Affairs

Sarah Campbell

## Division Planner/Director Disclosure

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

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**Designations of Credit**

NetCE designates this continuing education activity for 3 ANCC contact hours.



This activity was planned by and for the healthcare team, and learners will receive 3 Interprofessional Continuing Education (IPCE) credits for learning and change.

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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.



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

**INTRODUCTION**

The ability to remain upright on the varied terrain of the physical world, whether at rest or in motion, depends on the interplay of multiple faculties: awareness, vision, memory, balance, coordination, strength, and agility. These faculties are acquired and honed during youth and undergo an inexorable erosion during old age. Simple maneuvers, once negotiated effortlessly and with little conscious attention, become unpredictable and less reliable as one grows older. Witness an older man hurrying up a flight of stairs. At first nothing appears amiss, when suddenly the toe of his right shoe fails to clear the ledge of the next step and he trips forward in disbelief—this has never happened before. Imperceptible quadriceps atrophy and gradual general deconditioning likely accounts for the failure lifting the advancing foot just far enough to clear the step. Consider an older woman descending the same staircase cautiously, less sure whether she can negotiate every step-down safely, unaware that her hesitancy arises from the subtle changes in vision imposed by cataracts. The strength and agility required to maintain an upright posture while carrying out the usual tasks of work and play dissipate with age. Other factors can also contribute to deficits in the skills necessary to maintain balance and gait, including disorders of the nervous system, infection, muscular weakness/wasting, and intoxication.

Injuries sustained by falling, especially falls among older adults, can lead to immediate and long-term sequelae, including death. Health professionals responsible for hospital and long-term facility care have increasingly worked to develop programs that reduce fall risk among inpatients. Given the growing expansion of the aging population, it is equally important that primary care providers pay close attention to risk assessment and fall prevention among community-dwelling older adults. This course will review the epidemiology and scope of falls and fall-related injuries, available clinical guidance for screening and fall risk assessment, and management strategies for fall prevention in community and healthcare settings, emphasizing the fall burden associated with aging.

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## EPIDEMIOLOGY

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Falls and fall-related injuries are common worldwide and have the heaviest impact in low-income communities and communal settings with a preponderance of older adults. Falls can cause severe injury such as hip fractures and head trauma. Among older adults, injurious falls may heighten the risk for further loss of mobility and early death. The World Health Organization estimates that 37.3 million falls severe enough to require medical attention occur each year and notes that falls are the second leading cause of unintentional injury deaths worldwide, after road traffic injuries [7]. Because the number of falls is so high, the resultant loss of disability-adjusted life years (DALYs) is significant—more lives lived with disability than results from transport injury, drowning, burns, and poisoning combined [7]. Not only is the individual economic burden related to falls and fall injuries increasing, healthcare system costs have skyrocketed. Approximately 40% of the total DALYs lost due to falls globally occurs in children [7].

The Centers for Disease Control and Prevention (CDC) conducts surveillance of falls in the United States, including the incidence rate of reported falls by state. While there is variability in the fall rate per state, those with the highest recorded number of falls among older adults are California, Texas, and Florida [3]. CDC surveillance data indicate that about 30 million falls occur annually across the country, of which 37% require medical attention. Of those individuals needing medical treatment, many also need to restrict their activity for a minimum of one day. These data show that, on average, there are 8 million fall injuries per year in the United States [3].


Falling imposes an economic hardship not only for individual patients but also the healthcare system in general. Approximately 800,000 patients each year are hospitalized because of fall-related injuries. According to National Council on Aging estimates, the 2015 cost of nonfatal falls was documented at \$50 billion [4]. The cost related to fall treatment is expected to reach an estimated \$101 billion by 2030. Fatal falls incur nearly \$754 million in healthcare costs alone [4]. Individual

groups at highest risk of falling are those 65 years of age and older, young children, and women; men are at higher risk of death associated with falls [7].

### FALLS AMONG OLDER ADULTS

*Of falls that result in injury severe enough to require medical attention, what proportion require treatment for fracture?*

As noted, falls are a common occurrence in the frail older adult population, causing injuries that may result in disability, institutionalization (e.g., long-term care facility admission), or even death. Older adults are particularly prone to falling because of age-associated, gradual onset of lower body muscle weakness, disturbances of gait, and balance deficits. More than 14 million, or 1 in 4, older adults in the United States report falling every year. About 30% of falls result in injury severe enough to require medical attention; of these, approximately 50% require treatment for bone fracture. The most common skeletal fracture sites are the hip, spine, forearm, leg, pelvis, arm, and hand. Hip fractures from falling occur at the rate of about 1 per 100 falls in older adults, a serious complication that requires hospitalization, surgery, and often results in long-term disability. Even in the absence of injury, many older people who fall then develop a fear of falling, which may prompt additional restriction of physical activity, leading to further loss of physical fitness and agility, thereby increasing the risk of falling.



According to the World Falls Guidelines Task Force, clinicians should routinely ask about falls in their interactions with older adults, as they often will not be spontaneously reported.

(<https://academic.oup.com/ageing/article/51/9/afac205/6730755>. Last accessed March 26, 2024.)

**Strength of Recommendation/Level of Evidence:**  
1A (Strong recommendation based on high-quality evidence)

In 2020, emergency departments recorded 3 million visits for falls involving older adults; falls among adults older than 65 years of age caused more than 36,000 deaths, making it the leading cause of injury-related death in that age group [3]. Women are statistically more likely to report a fall injury compared with men of the same age. Most falls occur in the home (60%), followed by community public areas (30%) and healthcare settings (10%), such as hospitals and long-term care facilities [13]. Community-dwelling adults 65 years of age or older account for one-third of those who experience falls each year.

Fall risk increases gradually with aging, associated with onset of chronic diseases and eventually with the aging process itself. The most robust correlation with fall risk is found among those with comorbidities of the central nervous system, heart disease, rheumatoid disease, osteoporosis, and chronic pain [5]. Obesity is observed to convey an increased risk of falls, related to sarcopenia and coinciding with a more sedentary lifestyle as one ages [6]. A systematic review and meta-analysis confirmed that obesity increases the risk of falls and multiple falls in people 60 years of age and older; however, there was insufficient evidence of an association with fall-related injuries or fractures [8]. In fact, data collated from the subset of cohort studies suggested that obese older persons are actually less likely to experience a fall injury or hip fracture.

### FALLS AMONG CHILDREN

Among those 19 years of age or younger, falls are the most common cause of nonfatal injuries each year. Children younger than 6 years of age have the highest proportion of visits for falls, with 1.2 million emergency department visits per year [13]. Falls threaten the safety of children, and they are fourth among causes of unintentional death in children and adolescents. There is concern that childhood falls are under-reported events in health institutions [27].

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## TYPES OF FALLS

### *What are the three main categories of falls?*

Falls are defined by the World Health Organization as “events that result in a person coming to rest inadvertently on the ground, floor, or other lower level” [7]. Falls can be categorized into three types: physiological anticipated, physiological unanticipated, and accidental. It is important that the types of falls and risks of falling, whether living at home or residing in healthcare facilities, are well understood so appropriate fall prevention measures can be undertaken [9]. Fall prevention strategies designed for community-dwelling persons and healthcare facility inpatients and residents will be discussed later in this course.

The category of physiologically anticipated falls includes individuals who are at risk because of age and/or health status, as for example those with altered mental status, high-risk medication (e.g., sedative, epidural post-delivery), and frequent toileting needs (e.g., diarrhea, frequent urination) due to medications or intercurrent illness. Healthcare providers in the ambulatory setting as well as hospital and nursing home staff should be cognizant of individual risk and vigilant for the possibility of falls in this category. At-risk patients should be identified and closely monitored to address risk factors and ensure that preventive measures are in place [9]. Examples of anticipated falls include a patient with Parkinson disease falling from a toilet, a patient with dementia who falls trying to get up from bed, or a patient with a large volume loss having a syncopal episode in the bathroom unattended.

Unanticipated physiologic falls are fall events wherein the individual has no inherent (physiological) risk or reason for anticipating a fall under usual circumstances. In the inpatient/in-residence setting with fall protocols in place, these patients should be documented as low risk for falling [9]. Examples of patients who might experience this category fall event would be a patient who develops stroke symptoms while sitting in a chair, or a patient who has a syncopal episode while straining for a bowel movement in the bathroom. Patients with new-onset seizures would also belong in this type of fall category.

Accidental falls are those caused mainly by slips and trips, but other incidents could occur [9]. As an example, a hospital inpatient trips over the IV tubing or IV pump power cable, or another patient trips over the footrest of a wheelchair. These types of falls are accidental; whether or not they are predictable, thus preventable, depends on considerations of the environment, age, strength, and clinical condition [9].

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## FALL INJURIES AND REIMBURSEMENT

The Joint Commission (TJC) published a sentinel event alert to assist in preventing falls and fall-related injuries in healthcare settings. A sentinel event is “an unexpected occurrence involving death or serious physical or psychological injury, or the risk thereof” [10]. Falls resulting in serious injury or death are among the top 10 sentinel events reported to TJC. Of the 465 falls reported to TJC between 2009 and 2015, 63% resulted in death, while the remaining 37% resulted in injuries only [11].

### FALL INJURIES

Children between 0 and 5 years of age are learning new skills, such as walking and climbing, which can result in falls from ground level surfaces to several feet, such as off chairs or stairs. Many of these can result in serious injury, including open wounds, fractures, or even severe brain injury [13].

Fractures are a common injury in the older adult population, with approximately 20% sustaining major injuries (e.g., a head injury). Fractures of the hip occur in 1% of all falls in the older adult population [12]. While this is a small percentage, it significantly increases the risk of morbidity and mortality. After 65 years of age, the observed mortality rate within the first year after a hip fracture repair is 15% to 36%. A prospective cohort study of 728 patients who underwent surgery for hip fractures between 2013 and 2015 found that 121 died within one year post-fracture, a mortality rate of 17% [14]. One-year mortality risk following hip fracture was associated with the development of pressure ulcers, inability to recover pre-fracture ambulation, postoperative anemia, and the development of urosepsis [14].

As noted, other common fracture locations that result from falling are the proximal humerus, pelvis, distal radius, and vertebral bodies. Prosthetic fractures, which occur around joint replacement prostheses, have become more common in the older adult population as well [12]. Many require surgical intervention to repair. Femur fractures are common in the

older adult population related to falls. The overall functional decline of older adults post-femur fracture is 50% within the first year [12].

Falls are also the leading cause of traumatic brain injury in patients 65 years of age or older. The extent of head injuries resulting from a fall may be inapparent initially; delayed onset of symptoms and altered mentation may emerge over a few days post-fall [12]. Head injuries involving elderly patients warrant a careful history, taking into account the possibility of secondary hemorrhagic complications resulting from prior anticoagulant and antiplatelet drug usage. Subdural hematomas, subarachnoid hemorrhage, skull fractures, and diffuse axonal injury are all potential injuries. Management decisions for head injury should be based on a detailed history of the fall event itself, not just the patient's initial clinical presentation. Falls from different heights influence whether rapid assessment with head computed tomography (CT) imaging (within certain time frames) is advisable, especially if there are suspected open or depressed skull fractures, focal deficits, vomiting, or history of prior anticoagulants or antiplatelet medications [15]. The presence of any of these features warrants specialized care with neurosurgery consultation to ensure proper treatment and care is provided.

### FALL INJURY REIMBURSEMENT

Reimbursement to hospitals and long-term care facility for costs related to fall injuries is no longer covered by the Centers for Medicare and Medicaid Services (CMS) as of 2008 [16]. However, CMS does reimburse for fall risk assessments and fall prevention programs. Falls were not originally included in the CMS no-pay policy, and the addition of falls to the policy was originally questioned due to lack of supporting evidence of fall prevention efficacy. However, the decision was made to add falls to the no-pay policy in hopes of increasing research efforts to further prevent falls. The CMS has stated, "...we believe these types of injuries and trauma should not occur in the hospital, and we look forward to...identifying research... that will assist hospitals in following the appropriate steps to prevent these conditions from occurring after admission" [17].

Hospitals and clinics also cannot bill the patient for any services related to a "never event," such as a fall. Any injury costs incurred from a never-event fall (e.g., a humeral fracture) would not be billed to the patient, and the hospital would not receive reimbursement from Medicare regarding these services. They would still, however, receive reimbursement for the treatment received related to the original hospitalizing event (e.g., myocardial infarction) [18].

The National Council on Aging (NCOA) notes that although defined fall risk-related services, such as fall risk assessments, in the clinical setting may be lacking, providers should counsel their patients on potential risks of falling [17]. All healthcare providers can boost reimbursement to the hospital by providing and documenting that approximately 50% of a given daily visit was dedicated to education and or counseling on fall risk.

These reimbursements for patient education regarding fall risk also apply to Medicare Annual Wellness visits (initial and subsequent) and general offices for follow-ups or illnesses [17].

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## FALL RISKS

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### *Which fall risk factors are intrinsic?*

Personal fall risks can be organized into two categories: those associated with environmental (extrinsic) hazards and those related to age, general health, and mobility (intrinsic factors). Extrinsic factors include poor lighting, lack of personal ambulation aids (if needed), loose carpets, slippery floors, low objects (e.g., low toilets), steps, cords, or improper footwear. Intrinsic factors are those associated with aging, intoxication, and/or chronic disease, such as weakness, disturbances of gait and balance, declining vision, and medication side effects. Examples of intrinsic factors that lead to an increased risk of falling are gait abnormalities associated with Parkinson or vestibular diseases; bradycardia from beta blockers; drowsiness associated with sedative medication; reduced visual acuity from retinopathy or cataracts; hypotension (postural, medication induced, or hypovolemic); delirium and orthostatic instability related to acute infection and febrile states; and general loss of functional capacity associated with aging [2; 12].

Fall risk assessment and prevention is a matter of increasing concern for hospitals, given that falls among inpatients occur often, particularly in acute care settings [24]. One study demonstrated that the highest incidence of falling was among patients admitted with neurologic diagnoses; the lowest incidence of falls was among those on the surgical service. Important risk factors identified by the study were advanced age, emergency arrival, hospital-to-hospital transfers, and prolonged hospital stay [24]. Fall prevention in hospitals and long-term care facilities has been more difficult following the onset of the COVID-19 pandemic. Since 2020, patient-nurse ratios have increased, along with high turnover rates in organizations. High turnover rates and frequent change of staff have been associated with an increased incidence of adverse events, including increased fall rates, especially in nursing home settings [2]. This scenario is concerning, because staff who are not able to be fully aware of a resident's functional abilities are less apt to intervene with preventive measures or timely assistance [2].

Situational factors (e.g., activities, habits) can also impact fall risk associated with any setting and type of fall [12]. The likelihood of falling is dependent on a person's strength, agility, and capacity to maintain mobility and an upright posture in response to sudden situational challenges. Unfamiliarity when traversing new terrain or visiting new locations may also increase the risk of falling. Distractions (e.g., walking and talking at the same time), missing a step or curb, or rushing to get from place to place (e.g., the telephone or restroom) increase risk [12]. Fear of repeated falls can cause situational

anxiety that also increases risk of another fall. While falls are multifactorial, history of previous falls is the best predictor of the likelihood of future fall events.

## FALL RISK SCREENING, ASSESSMENT, AND INTERVENTION

Several approaches to fall prevention have been developed by specialty societies and public health agencies to assist care providers and healthcare systems reduce the likelihood of falls and fall-related injuries. Strategies differ somewhat in reference to the clinical context: those applicable to persons residing in the community and those applicable to patients residing in hospitals and long-term care facilities. However, certain interventions have been identified as useful in all residential settings, whether community or inpatient care facility [12]:

- Safety devices (e.g., grab handles, high friction floors, appropriate footwear)
- Regular exercise, leg muscle strengthening, gait training, and balance exercises
- Medication review and management
- Vitamin D supplementation to improve bone health and muscle strength
- Review of environmental issues, including evaluation of the current living conditions

## COMMUNITY FALL PREVENTION PRACTICES

The development of best practices for fall prevention in community-dwelling adults is the purview of primary care providers and centers on preventive care of the older adult patient. Reducing the risk of falls and fall injury in older adults is part of the CDC's Stopping Elderly Accidents, Deaths, & Injuries (SEADI) program [29]. The CDC SEADI program has developed clinical materials and a toolkit (assessment techniques) designed help care providers assess and manage risk in their older patients. Included is a streamlined algorithm for fall risk screening, assessment, and intervention (**Figure 1**). Office-based screening of older patients is recommended yearly, and a brief questionnaire is provided for this purpose. Patients identified as being at increased risk should receive an assessment for prior fall events and modifiable risk factors. SEADI has also developed an assessment protocol designed for evaluating functional strength and balance (e.g., Timed Up and Go Test; 4-Stage Balance Test), reviewing medication side effects, asking about home hazards (e.g., throw rugs, slippery tub floor), measuring orthostatic blood pressure (lying and standing positions), and checking for visual acuity. Specific interventions to reduce fall risk are guided by the results of risk assessment, paying attention to other factors such as footwear (e.g., shoe fit, traction, heel height), likelihood of vitamin D deficiency, and potential impact of comorbidities.

## Interventions

Exercise interventions are the cornerstone for fall risk reduction and prevention of fall-related injury in community-dwelling older adults. According to the U.S. Preventive Services Task Force (USPSTF), both supervised individual and group classes are effective when functional training is included [31]. Older adults should set a weekly goal of 150 minutes of moderate-intensity exercise (or 75 minutes of vigorous physical activity) combined with muscle-strengthening activities twice each week. A meta-analysis of 59 randomized trials found that fall prevention exercise programs are beneficial for adults at average or high risk of falls [32]. The rate of falls in this study was 23% lower among participants in an exercise program compared with those in control groups. Exercise programs effective in reducing falls are those that include functional exercises, balance training, and resistance exercises.

Other interventions for reducing fall risk are guided by the patient's individual fall risk assessment. Important considerations include prescription and over-the-counter medications that may result in side effects such as drowsiness, dizziness, and orthostatic hypotension; regular visual acuity testing at 1- to 2-year intervals, in order to update eyeglasses when needed and manage cataracts in a timely fashion; and improving home safety by eliminating tripping hazards, improving lighting, and adding grab bars in the tub or shower. Routine vitamin D and calcium supplementations have not been found effective, nor are they recommended by the USPSTF, for reducing fall risk in older adults without evidence of deficiency [30]. However, in select older women at risk for hip fracture, it may be prudent to consider calcium and vitamin D supplementation, screening for osteoporosis (recommended for all women older than 65 years of age), and weight-bearing exercises.



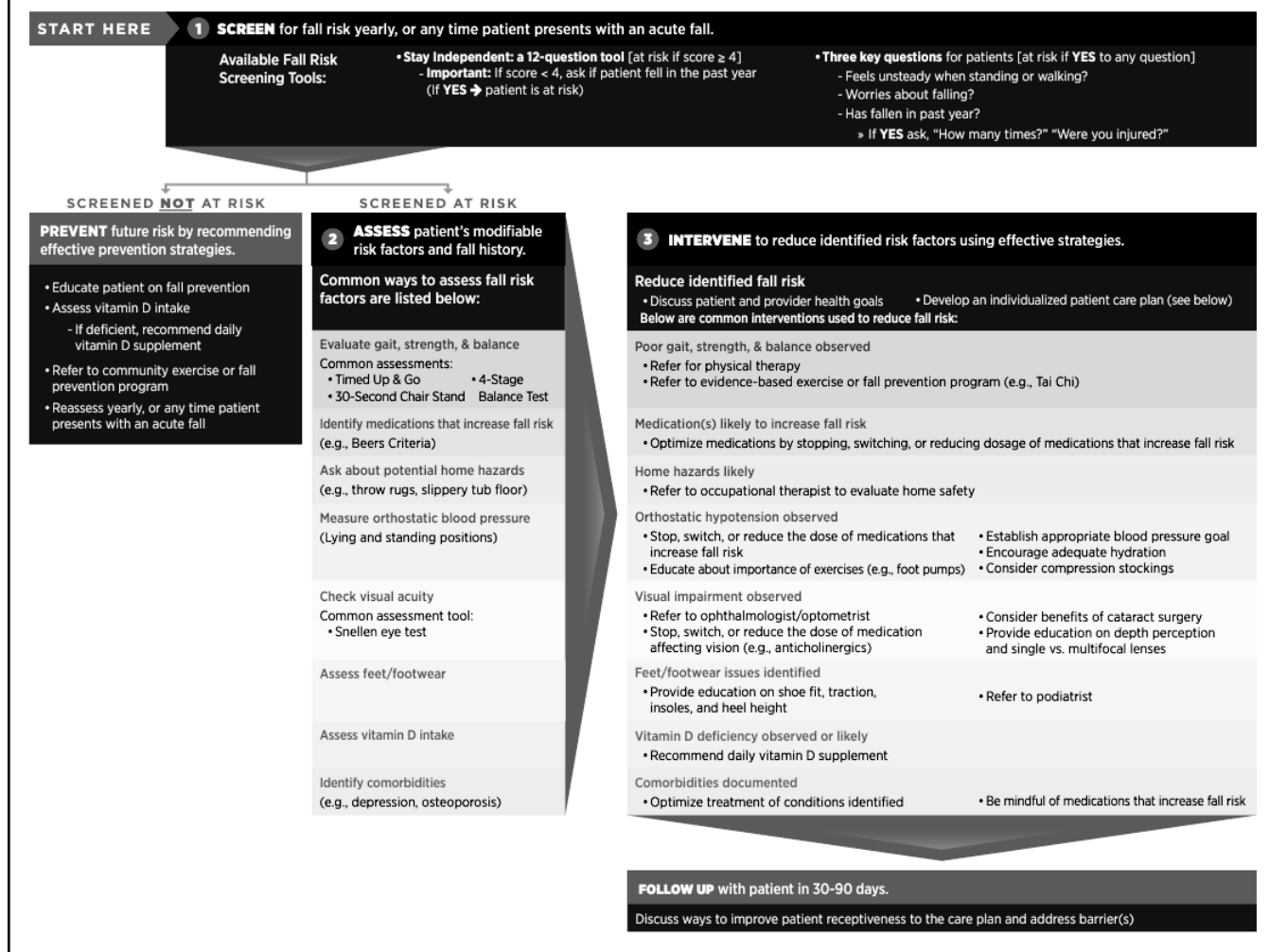
EVIDENCE-BASED  
PRACTICE  
RECOMMENDATION

The World Falls Guidelines Task Force recommends providing advice on how to maintain safe mobility and optimize physical functioning to older adults at low risk of falls from a clinician trained to do so. Such advice should consider the circumstances, priorities, preferences and resources of the older adult. This advice should reinforce health promotion/prevention messaging relevant to falls and fracture risks such as those on physical activity, lifestyle habits and nutrition including vitamin D intake.

(<https://academic.oup.com/ageing/article/51/9/afac205/6730755>. Last accessed March 26, 2024.)

**Strength of Recommendation/Level of Evidence:**  
E (Expert opinion)

## STADI ALGORITHM FOR FALL RISK SCREENING, ASSESSMENT, AND INTERVENTION AMONG COMMUNITY-DWELLING ADULTS 65 YEARS AND OLDER



Source: [29]

Figure 1

### INPATIENT AND RESIDENT FALL PREVENTION PRACTICES

*For inpatients or residents, when should fall risk assessment and preventive interventions start?*

The Agency for Healthcare Research and Quality (AHRQ) estimates that each year between 700,000 and 1 million people in the United States fall in the hospital [21]. Many of these falls cause fractures, lacerations, or internal bleeding, leading to increased healthcare utilization. Fall prevention involves managing a patient's underlying fall risk factors and optimizing the facility's physical design and environment [21]. The AHRQ has developed hospital training programs, a fall prevention toolkit, and other materials to help inpatient facilities overcome the challenges associated with developing, implementing, and sustaining a fall prevention program [21].

Fall risk assessment and preventive interventions should start at initial admission to the hospital or long-term care facility. Within hospitals, bed alarms, sitters, and physical restraint orders have been used in the past to reduce the likelihood of patients falling [17]. However, restraints have been noted to pose an increased risk for severe injury (and aspiration) and are used only very rarely. Restraints must have 1:1 observation and a physician order [28]. While employing a bedside sitter seems a reasonable precaution, one study found that evidence is inconclusive whether the presence of a sitter decreases the number of falls [16].

While many precautions are of benefit to all patients in preventing falls, the AHRQ recommends fall prevention measures should be individualized, considering the patient's age, fall history, and risk factors. The goal is to assure patient safety from falls, preventing additional harm during the period of hospitalization. Outpatient clinic administrators and staff can



use similar prevention measures to ensure patient safety against falls in the home [21]. Although the following precautions were developed for reducing risk of inpatient falls, they may be applicable to the ambulatory clinic and home environment as well [21]:

- A call light within reach and instruction to the patient on proper use
- Sturdy handrails in restrooms, patient rooms, and hallways
- Hospital or exam tables in the lowest position, with brakes locked
- Wheelchair locks used when inactive
- Appropriate footwear (e.g., nonskid soles, avoiding slippers with open backs or open-toed sandals)
- Appropriate supplemental lighting
- Clean and dry flooring
- Safe handling practices of patients, including assistance with transferring and ambulation

### Fall Prevention Programs

Inpatient or resident fall prevention programs have been implemented broadly, often in association with regular exercise routines for residents of long-term care facilities. Hospital interventions have been demonstrated as effective for decreasing fall rates [20]. The AHRQ Fall Prevention in Hospitals training program supports staff in the development and implementation of their own fall prevention programs with standardized tools to prevent falls [21]. The training consists of five modules with various practices, including information on why change is needed and how to manage change, best practices in fall prevention, how to implement the program, and how to measure fall rates [21]. The AHRQ training program also addresses discharge planning, including strategies for fall prevention after discharge of at-risk patients back into the community.

In addition, the CDC STEADI initiative includes a fall prevention toolkit specifically designed for inpatient use. This was developed to help inpatient organizations integrate fall prevention programs into their current practices. The STEADI initiative includes 10 practical steps identified by research findings and provider practices to [22]:

- Reduce patient falls during and after hospital stays
- Foster better partnership with outside providers for post-hospital discharge care
- Upgrade hospital practices and records
- Recognize and appropriately manage medications that place patients at an increased fall risk

The STEADI initiative also outlines suggested tasks for all members of the interprofessional team in support of safe mobility and fall prevention (*Table 1*).

The NCOA has initiatives for fall prevention programs that are geared toward the home settings. This Falls Free Initiative is led by the National Falls Prevention Resource Center. The Falls Free Initiative works with more than 70 organizations nationwide to develop strategies to prevent falls, fall-related injuries, and fall-related deaths. The Falls Free Initiative can be accessed online at <https://www.ncoa.org/article/get-the-facts-on-falls-prevention> [23].

### PEDIATRIC FALL PREVENTION

The Humpty Dumpty Falls Scale (HDFS) serves as an international tool to help assess pediatric fall risk. Developed in Brazil, this tool is used within the inpatient setting with patients birth to 21 years of age. The parameters include age, gender, diagnosis, impairments, environmental factors, response to surgery/anesthesia (if applicable), and medication usage responses are scored on a 1–4 scale. Scores less than 12 indicate low risk, while scores of 12 or greater are considered at high risk for falls. The HDFS is used at admission, daily, and with any changes in level of care [27].

## CONCLUSION

Falling is among life's earliest and most common experiences. Is there anyone who has not fallen while learning to walk, or not stumbled when in too much of a hurry? When we are young, like "Jack and Jill (who) went up the hill to fetch a pail of water," falling can be painful but is often of little consequence to life and limb; moreover, falling down teaches resilience and the importance of being careful. Jack and Jill likely jumped up no worse for the wear and later went right back up the hill again. It is worth noting here that these two were out and about, active at play or doing chores. The tale of Jack and Jill connotes youth, energy, exuberance, companionship; their danger of falling came from being too much in a hurry.

Humpty Dumpty, on the other hand, tells a more somber tale. He was not out and about at all, just simply sitting on the wall; and when he fell it was a "great fall" (of serious consequence). All the king's horses and all the king's men couldn't put Humpty together again! Perhaps Humpty Dumpty is a nursery rhyme for the aging, a cautionary tale on the importance of staying active and the hidden danger in simply sitting still. Humpty Dumpty can connote age, inactivity, weight gain, solitude, and fragility. Sedentary life has the appearance of safety but the place where one sits is not always safe, and the consequences of falling can be dire.

**SUGGESTED TASKS FOR SAFE MOBILITY AND FALL PREVENTION  
PROGRAM TEAM MEMBERS**

Team Member	Suggested Tasks
STEADI safe mobility champion (from any profession)	<ul style="list-style-type: none"> <li>• Proactively encourage early mobilization of patients to reduce fall risks during hospitalization</li> <li>• Work with team to incorporate the safe mobility and fall prevention program into the patient care workflow</li> <li>• Work with available unit-based or hospital educators to establish a training program for current and future employees</li> <li>• Be available to troubleshoot issues during implementation</li> <li>• Provide feedback to team members</li> <li>• Monitor and report results of program implementation</li> <li>• Communicate with hospital leadership about the program</li> <li>• Assign and train staff to discuss fall prevention strategies with patients and caregivers</li> </ul>
Nurse and/or certified nursing assistant	<ul style="list-style-type: none"> <li>• Screen patients for fall risk using a screening tool (e.g., Stay Independent checklist, three key questions, STRATIFY Risk Assessment Tool)</li> <li>• Perform gait testing (e.g., Timed Up and Go Test, 30-Second Chair Stand Test, or 4-Stage Balance Test)</li> <li>• Check orthostatic blood pressure</li> <li>• Educate patients about orthostatic hypotension and related fall risk</li> <li>• Discuss fall prevention strategies with patients and caregivers</li> <li>• Perform vision assessment (e.g., Snellen eye chart)</li> <li>• Counsel about using single distance lenses when walking outside (e.g. avoid bifocals)</li> <li>• Assess feet and footwear</li> <li>• Conduct cognitive assessment (e.g., Mini-Cog)</li> <li>• Ensure each patient has optimal independence in instrumental activities of daily living (IADLs) and activities of daily living (ADLs) during hospital stay</li> <li>• Mobilize patient at least three times a day as tolerated</li> <li>• Give patient appropriate STEADI patient educational materials</li> <li>• Follow up during their hospital stay to ensure patients are making progress as part of fall prevention care plan</li> </ul>
Physician, nurse practitioner, physician assistant, clinical nurse specialist	<ul style="list-style-type: none"> <li>• Take a fall history, including circumstances of previous falls</li> <li>• During physical exam include an observation of gait to identify medical issues that could increase fall risk (e.g., cardiac or neurologic disease)</li> <li>• Review results of fall risk assessments performed by other team members</li> <li>• Avoid prescribing and manage medications that increase fall risk (collaborate with pharmacists)</li> <li>• Order appropriate labs and imaging specific to fall risk</li> <li>• Recommend and provide referrals specific to fall risk</li> <li>• Discuss fall prevention strategies with patients and caregivers</li> <li>• Engage patients and caregivers in developing and implementing individual fall prevention care plans</li> <li>• Avoid issuing bed rest orders or discontinue them as soon as not clinically indicated</li> <li>• Discontinue tethers (IV lines, urinary catheters, etc.) as soon as not clinically indicated</li> <li>• Recommend community exercise or fall prevention programs</li> </ul>
Pharmacist	<ul style="list-style-type: none"> <li>• Review medications to identify those that increase fall risk</li> <li>• Notify safe mobility and fall prevention program team of any medications that might increase fall risk and set up alerts to providers for those medications</li> <li>• Make recommendations for dose reduction or safer alternatives for medications that increase fall risk</li> <li>• Raise awareness about medication-related fall risks</li> <li>• Discuss fall prevention strategies with patients and caregivers</li> </ul>

*Table 1 continues on next page.*



**SUGGESTED TASKS FOR SAFE MOBILITY AND FALL PREVENTION  
PROGRAM TEAM MEMBERS (Continued)**

Team Member	Suggested Tasks
Physical therapist	<ul style="list-style-type: none"> <li>• Assess or inquire about baseline functional status</li> <li>• Discuss fall prevention strategies with patients and caregivers</li> <li>• Perform detailed gait and balance testing</li> <li>• Design a rehabilitation care plan or exercise program to improve mobility and balance during hospitalization</li> <li>• Educate patients about community-based fall prevention programs, such as tai chi classes or Stepping On</li> </ul>
Occupational therapist	<ul style="list-style-type: none"> <li>• Discuss fall prevention strategies with patients and caregivers</li> <li>• Educate patients about home trip hazards (e.g. throw rugs, stairs)</li> <li>• Recommend fall prevention safety features (e.g., grab bars, lighting, railings)</li> <li>• Educate patients and caregivers about behavioral and functional changes that impact fall risk</li> </ul>
<i>Source: [22]</i>	

Table 1

Falls are common in older adults, and the risk of falling increases with aging. While this course has focused on the older adult population, persons of all ages can be at risk for falls for a variety of reasons. Preventive measures can be used for any adult and all patients with limited mobility. Strategies for effective prevention of falls begin with proper assessment of predisposing factors and comorbidities, focusing on managing extrinsic and intrinsic factors that increase risk. Timely education of patients and families is recommended in the primary and secondary prevention of falls. By striving for the goal of zero falls, healthcare facilities and providers can achieve a significant reduction in number of injuries and loss of life. A given patient's fall risk can be reduced significantly in a single healthcare contact, using a prepared strategy (e.g., STEADI algorithm) to address potential medication side effects and need for vitamin D; home safety review, visual acuity testing, and lower body strength and balance testing; and education and advice regarding regular exercise for maintaining strength and mobility. Select patients benefit from referral to physical and/or occupational therapy for training to improve balance.

## RESOURCES

### CDC STEADI Initiative

This site provides links to office-based clinical tools and functional assessment instruction, including video demonstration.  
<https://www.cdc.gov/steady/materials.html>

### *Algorithm for Fall Risk Screening, Assessment, and Intervention*

<https://www.cdc.gov/steady/pdf/STEADI-Algorithm-508.pdf>

### *Timed Up and Go (TUG) Test*

<https://www.cdc.gov/steady/pdf/STEADI-Assessment-TUG-508.pdf>

### *4-Stage Balance Test*

<https://www.cdc.gov/steady/pdf/STEADI-Assessment-4Stage-508.pdf>

### National Institute on Aging

This site provides educational and instructive articles for aging adults, including exercises with video instruction for enhancing strength and balance.

<https://www.nia.nih.gov/health/exercise-and-physical-activity>

**Customer Information and Evaluation are located on pages 79–80.**

# Intercultural Competence and Patient-Centered Care

## Audience

This course is designed for all members of the interprofessional healthcare team.

## Course Objective

The purpose of this course is to provide members of the interprofessional healthcare team with the knowledge, skills, and strategies necessary to provide culturally competent and responsive care to all patients.

## Learning Objectives

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

1. Define cultural competence, implicit bias, and related terminology.
2. Outline social determinants of health and barriers to providing care.
3. Discuss best practices for providing culturally competent care to various patient populations.
4. Discuss key aspects of creating a welcoming and safe environment, including avoidance of discriminatory language and behaviors.

## 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.

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.

## 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

Mary Franks, MSN, APRN, FNP-C

## Senior Director of Development and Academic Affairs

Sarah Campbell

## Division Planner/Director Disclosure

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

## Accreditations & Approvals



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## Designations of Credit

NetCE designates this continuing education activity for 4 ANCC contact hours.



IPCE CREDIT™

This activity was planned by and for the healthcare team, and learners will receive 4 Interprofessional Continuing Education (IPCE) credits for learning and change.

NetCE designates this continuing education activity for 4.8 hours for Alabama nurses.

AACN Synergy CERP Category B.

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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.



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

## INTRODUCTION

Culturally competent care has been defined as “care that takes into account issues related to diversity, marginalization, and vulnerability due to culture, race, gender, and sexual orientation” [1]. A culturally competent person is someone who is aware of how being different from the norm can be marginalizing and how this marginalization may affect seeking or receiving health care [1]. To be effective cross-culturally with any diverse group, healthcare professionals must have awareness, sensitivity, and knowledge about the culture involved, enhanced by the use of cross-cultural communication skills [2; 3].

Healthcare professionals are accustomed to working to promote the healthy physical and psychosocial development and well-being of individuals within the context of the greater community. For years, these same professionals have been identifying at-risk populations and developing programs or making referrals to resources to promote the health and safety of at-risk groups. But, because of general assumptions, persistent stereotypes, and implicit and explicit biases, culture-related healthcare disparities persist [2]. In the increasingly diverse landscape of the United States, assessing and addressing culture-related barriers to care are a necessary part of health care. This includes seeking to improve one’s cultural competence and identifying blind spots and biases.

## DEFINITIONS

### CULTURAL COMPETENCE

In healthcare, 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 [4]. 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

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 [5]. Cultural humility is a lifelong process involving reflexivity, self-evaluation, and self-critique [6].

## DISCRIMINATION

Discrimination has traditionally been viewed as the outcome of prejudice [7]. It encompasses overt or hidden actions, behaviors, or practices of members in a dominant group against members of a subordinate group [8]. Discrimination has also been further categorized as lifetime, which consists of major discreet discriminatory events, or everyday, which is subtle, continual, and part of day-to-day life and can have a cumulative effect on individuals [9].

## 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” [10]. Diversity is often incorrectly conceptualized into singular dimensions as opposed to multiple and intersecting diversity factors [11].

## 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 inter-related and interact to create a whole [12]. This term also encompasses the ways that different types and systems of oppression intersect and affect individuals.

## PREJUDICE

Prejudice is a generally negative feeling, attitude, or stereotype against members of a group [13]. It is important not to 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” [13]. Prejudice stems from the process of ascribing every member of a group with the same attributes [14].

## 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” [15]. 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 [16]. 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 [17; 18].

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## BIAS: IMPLICIT AND EXPLICIT

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### *What are risk factors in triggering implicit biases for health professionals?*

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 [19]. 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 [20]. 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 [21; 22; 23; 24]. Some have asserted that the cognitive processes that dictate implicit and explicit biases are separate and independent [24].

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 [25]. 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 [26]. According to Georgetown University’s National Center on Cultural Competency, social characteristics that can trigger implicit biases include [27]:

- Age
- Disability
- Education
- English language proficiency and fluency
- Ethnicity
- Health status
- Disease/diagnosis (e.g., human immunodeficiency virus [HIV])
- 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 [20; 28]. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages [28].

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 [21].

Specific conditions or environmental risk factors have been associated with an increased risk for certain implicit biases, including [130; 131]:

- 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

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## ROLE OF INTERPROFESSIONAL COLLABORATION AND PRACTICE

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The study of implicit bias is appropriately interdisciplinary, representing social psychology, medicine, health psychology, neuroscience, counseling, mental health, gerontology, gender/sexuality studies, religious studies, and disability studies [28]. Therefore, implicit bias empirical research and curricula training development lends itself well to interprofessional collaboration and practice (ICP).

The main characteristics of ICP allow for implicit and explicit biases to be addressed by the interprofessional team. One of the core features of ICP is sharing—professionals from different disciplines share their philosophies, values, perspectives, data, and strategies for planning of interventions [29]. ICP also involves the sharing of roles, responsibilities, decision making, and power [30]. Everyone on the team employs their expertise, knowledge, and skills, working collectively on a shared, patient-centered goal or outcome [30; 31].

Another feature of ICP is interdependency. Instead of working in an autonomous manner, each team member's contributions are valued and maximized, which ultimately leads to synergy [29]. At the heart of this are two other key features: mutual trust/respect and communication [31]. 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 [32]. This includes [32]:

- 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.
- 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 [33]. 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 [33].

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## SOCIAL DETERMINANTS OF HEALTH

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### *What are the categories of social determinants?*

Social determinants of health are the conditions in the environments where people are born, live, learn, work, play, worship, and age that affect a wide range of health, functioning, and quality-of-life outcomes and risks. These circumstances are shaped by the distribution of money, power, and resources at global, national, and local levels. Healthy People 2030 groups social determinants of health into five categories [34]:

- Economic stability
- Education access and quality
- Health care access and quality
- Social and community context
- Neighborhood and built environment

These factors have a major impact on people's health, well-being, and quality of life. Examples of social determinants of health include [34]:

- Safe housing, transportation, and neighborhoods
- Racism, discrimination, and violence
- Education, job opportunities, and income
- Access to nutritious foods and physical activity opportunities
- Polluted air and water
- Language and literacy skills

Social determinants of health also contribute to wide health disparities and inequities. For example, people who lack access to grocery stores with healthy foods are less likely to have good nutrition, which raises the risk of heart disease, diabetes, and obesity and lowers life expectancy compared with those who have easier access to healthy foods [34].

Promoting healthy choices will not eliminate these and other health disparities. Instead, public health organizations and their partners must take action to improve the conditions in people's environments. Healthcare providers play a role by identifying factors affecting the health of their patients, providing resources (when appropriate), and advocating for healthy environments.

### ECONOMIC STABILITY

In the United States, 1 in 10 people live in poverty, and many people are unable afford healthy foods, health care, and housing. People with steady employment are less likely to live in poverty and more likely to be healthy, but many people have trouble finding and keeping a job. People with disabilities, injuries, or chronic conditions (e.g., arthritis) may be especially limited in their ability to work. In addition, many people with steady work still do not earn enough to afford the things they need to stay healthy [34].

Employment programs, career counseling, and high-quality childcare opportunities can help more people find and keep jobs. In addition, policies to help people pay for food, housing, health care, and education can reduce poverty and improve health and well-being [34].

### HEALTH CARE ACCESS AND QUALITY

Many people in the United States are unable to access the healthcare services they need. About 1 in 10 people in the United States lack health insurance, and people without insurance are less likely to have a primary care provider and be able to afford the healthcare services and medications they need. Strategies to increase insurance coverage rates are critical for making sure more people get important healthcare services, including preventive care and treatment for chronic illnesses [34].

In some cases, patients are not recommended health care services (e.g., cancer screenings) because they do not have a primary care provider or because they live too far away from healthcare providers who offer them. Interventions to increase access to healthcare professionals and improve communication—in person or remotely—can help more people get the care they need [34].

### SOCIAL AND COMMUNITY CONTEXT

People's relationships and interactions with family, friends, co-workers, and community members can have a major impact on their health and well-being. Many people face challenges and dangers they are not able to control, including unsafe neighborhoods, discrimination, or trouble affording the things they need. This can have a negative impact on health and safety throughout life.

Positive relationships at home, at work, and in the community can help reduce these negative impacts. But some people (e.g., children whose parents are in jail, adolescents who are bullied) often do not get support from loved ones or others. Interventions to help people access the social and community support they need are critical for improving health and well-being [34]. Healthy People 2030 objectives in this category focus on increasing the proportion of children and adolescents who have an adult they can talk to about serious problems, improving community health literacy, increasing the likelihood that an individual talks to friends or family about their health, and expanding access to online healthcare services [34].

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## BARRIERS TO PROVIDING CARE

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Culturally diverse patients experience a variety of barriers when seeking health and mental health care, including:

- Immigration status
- Lower socioeconomic status
- Language barriers
- Cultural differences
- Lack of or poor health insurance coverage
- Fear of or experiences with provider discrimination
- Mistrust of healthcare systems

Such obstacles can interfere with or prevent access to treatment and services, compromise appropriate referrals, affect compliance with recommendations, and result in poor outcomes. Culturally competent providers build and maintain rich referral resources to meet patients' assorted needs.

Encountering discrimination when seeking health or mental health services is a barrier to optimal care and contributor to poorer outcomes in under-represented groups. Some providers will not treat patients because of moral objections, which can affect all groups, but particularly those who are gender and/or sexual minorities, religious minorities, and/or immigrants. In

fact, in 2016, Mississippi and Tennessee passed laws allowing health providers to refuse to provide services if doing so would violate their religious beliefs [35]. However, it is important to remember that providers are obligated to act within their profession's code of ethics and to ensure patients receive the best possible care.

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## BEST PRACTICES FOR CULTURALLY RESPONSIVE CARE

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The U.S. Department of Health and Human Services has outlined steps important to incorporate in evaluation and treatment planning processes to ensure culturally competent clinical and programmatic decisions and skills [36].

The first step is to engage patients. In nonemergent situations, it is important to establish rapport before asking a series of assessment questions or delving deeply into history taking. Providers should use simple gestures as culturally appropriate (e.g., handshakes, facial expressions, greetings) to help establish a first impression. The intent is that all patients feel understood and seen following each interaction. Culturally responsive interview behaviors and paperwork should be used at all times [36].

When engaging in any patient teaching, remember that individuals may be new to the specific language or jargon and expectations of the diagnosis and care process. Patients should be encouraged to collaborate in every step of their care. This consists of seeking the patient's input and interpretation and establishing ways they can seek clarification. Patient feedback can then be used to help identify cultural issues and specific needs. If appropriate, collaboration should extend to include family and community members.

Assessment should incorporate culturally relevant themes in order to more fully understand patients and identify their cultural strengths and challenges. Themes include [36]:

- Immigration history
- Cultural identity and acculturation
- Membership in a subculture
- Beliefs about health, healing, and help-seeking
- Trauma and loss

In some cases, it may be appropriate and beneficial to obtain culturally relevant collateral information, with the patient's permission, from sources other than the patient (e.g., family or community members) to better understand beliefs and practices that shape the patient's cultural identity and understanding of the world.

Practitioners should work to identify screening and assessment tools that have been translated into or adapted for other languages and have been validated for their particular population group(s). An instrument's cultural applicability to

the population being served should be assessed, keeping in mind that research is limited on the cross-cultural applicability of specific test items or questions, diagnostic criteria, and concepts in evaluative and diagnostic processes [36].

Typically, culturally responsive care establishes holistic treatment goals that include objectives to improve physical health and spiritual strength; utilizes strengths-based strategies that fortify cultural heritage, identity, and resiliency; and recognizes that treatment planning is a dynamic process that evolves along with an understanding of patient history and treatment needs.

In addition to these general approaches, specific considerations may be appropriate for specific populations. While discussion of every possible patient subgroup is outside of the scope of this course, some of the most common factors are outlined in the following sections [36].

### RACIAL BACKGROUNDS

Race and color impact the ways in which individuals interact with their environments and are perceived and treated by others. Race is defined as groups of humans divided on the basis of inherited physical and behavioral differences. As part of the cultural competence process and as a reflection of cultural humility, practitioners should strive to learn as much as possible about the specific racial/ethnic populations they serve [37]. However, considerable diversity exists within any specific culture, race, or ethnicity [37]. Cultural beliefs, traditions, and practices change over time, both through generations and within an individual's lifetime. It is also possible for the differences between two members of the same racial/ethnic group to be greater than the differences between two people from different racial/ethnic groups. Within-group variations in how persons interact with their environments and specific social contexts are also often present.

As with all patients, it is vital to actively listen and critically evaluate patient relationships. All practitioners should seek to educate themselves regarding the experiences of patients who are members of a community that differs from their own. Resources and opportunities to collaborate may be available from community organizations and leaders.


Finally, preferred language and immigration/migration status should be considered. Interpreters should be used when appropriate, with adherence to best practices for the use of interpretation services. Stressing confidentiality and privacy is particularly important for undocumented workers or recent immigrants, who may be fearful of deportation.

### Black Patients

"Black" or "African American" is a classification that serves as a descriptor; it has sociopolitical and self-identification ramifications. The U.S. Census Bureau defines African Americans or Black Americans as persons "having origins in any of the Black racial groups of Africa" [38].

According to the U.S. Census, African Americans number 46.9 million as of 2020 [39]. By 2060, it is projected they will comprise 17.9% of the U.S. population [40]. This group tends to be young; 30% of the African American population in the United States is younger than 18 years of age. In 2019, the median age for this group was 35 years [41]. In terms of educational attainment, 89.4% of African Americans 25 years of age or older had a high school diploma or completed college in 2020 [39]. Texas has the largest African American population, at 3.9 million [41].

Historical adversity and institutional racism contribute to health disparities in this group. For the Black population, patient assessment and treatment planning should be framed in a context that recognizes the totality of life experiences faced by patients. In many cases, particularly in the provision of mental health care, equality is sought in the provider-patient relationship, with less distance and more disclosing. Practitioners should assess whether their practices connect with core values of Black culture, such as family, kinship, community, and spirituality. Generalized or Eurocentric treatment approaches may not easily align with these components of the Black community [42]. Providers should also consider the impact of racial discrimination on health and mental health among Black patients. Reports indicate that expressions of emotion by Black patients tend to be negatively misunderstood or dismissed; this reflects implicit or explicit biases.



When providing mental health services for African Americans, the American Psychiatric Association recommends exploring how a patient's present experiences connect to historical trauma for a particular group or community.

(<https://www.psychiatry.org/psychiatrists/diversity/education/stress-and-trauma/african-americans>. Last accessed September 26, 2023.)

**Level of Evidence:** Expert Opinion/Consensus Statement

### Asian Patients

As of 2019, 22.9 million Americans identified as Asian [43]. Between 2000 and 2019, Asians experienced the greatest growth compared with any other racial group at 81% [44; 45]. The Chinese group represents the largest Asian subgroup in the United States, and it is projected that this population will grow to 35.7 million between 2015 and 2040 [46; 47]. In 2019, Chinese Americans (excluding Taiwanese Americans) numbered at 5.2 million [43]. They also have the highest educational attainment; 54.6% of Asians 25 years of age or older had a bachelor's degree or higher in 2019 [43].

"Asian" is a single term widely used to describe individuals who have kinship and identity ties to Asia, including the Far East, Southeast Asia, and the Indian subcontinent [48]. This encompasses countries such as China, Japan, Korea, Vietnam, Cambodia, Thailand, India, Pakistan, and the Philippines. Pacific Islander is often combined with Asian American in census data. The Pacific Islands include Hawaii, Guam, Samoa, Fiji, and many others [48]. There are more than 25 Asian/Pacific Islander groups, each with a different migration history and widely varying sociopolitical environments in their homelands [49].

Asian American groups have differing levels of acculturation, lengths of residency in the United States, languages, English-speaking proficiency, education attainment, socioeconomic statuses, and religions. For example, there are approximately 32 different languages spoken among Asian Americans, and within each Asian subgroup (e.g., Chinese), multiple dialects may be present [49; 50]. In 2019, California had the largest Asian American population, totaling 5.9 million [44].

Recommended best practices when caring for Asian American patients include:

- Create an advisory committee using representatives from the community.
- Incorporate cultural knowledge and maintain flexible attitudes.
- Provide services in the patients' primary language.
- Develop culturally specific questionnaires for intake to capture information that may be missed by standard questionnaires.
- Emphasize traditional values and incorporate traditional practices (e.g., acupuncture) into treatment plans, when appropriate and desired.
- Explore patient coping mechanisms that draw upon cultural strengths.

### Latino/a/x or Hispanic Patients

In 2020, the Hispanic population in the United States numbered 60.6 million [51]. The majority of the Hispanic population in the United States (63.3%) identify themselves as being of Mexican descent [53]. Approximately 27% of the U.S. Hispanic population identify as Puerto Rican, Cuban, Salvadoran, Dominican, Guatemalan, Colombian, Honduran, Ecuadorian, or Peruvian [54].

In 2020, the Hispanic population comprised 18.7% of the U.S. population [51]. As such, they are the largest ethnic minority group in the United States. By 2060, Hispanics are expected to represent 31% of the U.S. population [55]. They are also a young group, with a median age of 29.8 years [51]. In 2019, the three states with the largest Hispanic population growth were Texas (2 million), California (1.5 million), and Florida (1.4 million); these three states have the largest Hispanic populations overall [52].



When involved in the care of Latinx/Hispanic individuals, practitioners should strive to employ *personalismo* (warm, genuine communication) and recognize the importance of *familismo* (the centrality of the family). More flexible scheduling strategies may be more successful with this group, if possible, and some patients may benefit from culturally specific treatment and ethnic and gender matching with providers. Aspects of Latino culture can be assets in treatment: strength, perseverance, flexibility, and an ability to survive.


### Native American Patients

The Native American population is extremely diverse. According to the U.S. Census, the terms “Native American,” “American Indian,” or “Alaskan Native” refer to individuals who identify themselves with tribal attachment to indigenous groups of North and South America [56]. In the United States, there are 574 federally recognized tribal governments and 324 federally recognized reservations [57].

In 2020, it was reported that there were 7.1 million Native Americans in the United States, which is approximately 2% of the U.S. population [57]. By 2060, this number is projected to increase to 10.1 million, or 2.5% of the total population [57].

In general, this group is young, with a median age of 31 years, compared with the general median age of 37.9 years [58]. As of 2018, the states with the greatest number of residents identifying as Native American are Alaska, Oklahoma, New Mexico, South Dakota, and Montana [59]. In 2016, this group had the highest poverty rate (26.2%) of any racial/ethnic group [58].

Listening is an important aspect of rapport building with Native American patients, and practitioners should use active listening and reflective responses. Assessments and histories may include information regarding patients’ stories, experiences, dreams, and rituals and their relevance. Interruptions and excessive questioning should be avoided if at all possible. Extended periods of silence may occur, and time should be allowed for patients to adjust and process information. Practitioners should avoid asking about family or personal matters unrelated to presenting issues without first asking permission to inquire about these areas. Native American patients often respond best when they are given suggestions and options rather than directions.



The American Psychological Association recommends that clinicians aim to understand and encourage Indigenous/ethnocultural sources of healing within professional practice.

(<https://www.apa.org/about/policy/guidelines-race-ethnicity.pdf>. Last accessed September 26, 2023.)

**Level of Evidence:** Expert Opinion/Consensus Statement

### White American Patients

In 2021, 76.3% of the U.S. population identified as White alone [60]. The U.S. Census Bureau defines White race as person having origins in any of the original peoples of Europe, the Middle East, or North Africa [38]. While the proportion of population identifying as White only has decreased between 2010 and 2020, the numbers of persons identifying as White and another race/ethnicity increased significantly. The White population in the United States is diverse in its religious, cultural, and social composition. The greatest proportion of this group reports a German ancestry (17%), followed by Irish (13%), English (10%), and Italian (7%) [61].

Providers can assume that most well-accepted treatment approaches and interventions have been tested and evaluated with White American individuals, particularly men. However, approaches may need modification to suit class, ethnic, religious, and other factors.

Providers should establish not only the patient’s ethnic background, but also how strongly the person identifies with that background. It is also important to be sensitive to persons multiracial/multiethnic heritage, if present, and how this might affect their family relationships and social experiences. Assumption of White race should be avoided, as White-passing persons of color have their own unique needs.

### Multiracial Patients

Racial labels do not always have clear meaning in other parts of the world; how one’s race is defined can change according to one’s current environment or society. A person viewed as Black in the United States can possibly be viewed as White in Africa. Racial categories also do not easily account for the complexity of multiracial identities. An estimated 3% of United States residents (9 million individuals) indicated in the 2010 Census that they are of more than one race [149]. The percentage of the total United States population who identify as being of mixed race is expected to grow significantly in coming years, and some estimate that it will rise as high as one in five individuals by 2050 [36; 150].

Multiracial individuals often report feeling not fully embraced by any racial or ethnic group, and mistaken identity is a common issue. A small study of multiracial patients assessed their healthcare experiences and noted six commonly encountered microaggressions: mistaken identity, mistaken relationships, fixed forms, entitled examiner, pervasive stereotypes, and intersectionality [144]. It is important to avoid assuming race/culture based only on appearance and to take into account the patient’s self-reported identity.

### RELIGIOUS, CULTURAL, AND ETHNIC BACKGROUNDS

Religion, culture, beliefs, and ethnic customs can influence how patients understand health concepts, how they take care of their health, and how they make decisions related to their health. Without proper training, clinicians may deliver medical

advice without understanding how health beliefs and cultural practices influence the way that advice is received. Asking about patients' religions, cultures, and ethnic customs can help clinicians engage patients so that, together, they can devise treatment plans that are consistent with the patients' values [37].

Respectfully ask patients about their health beliefs and customs and note their responses in their medical records. Address patients' cultural values specifically in the context of their health care. For example, one may ask [37]:

- "Is there anything I should know about your culture, beliefs, or religious practices that would help me take better care of you?"
- "Do you have any dietary restrictions that we should consider as we develop a food plan to help you lose weight?"
- "Your condition is very serious. Some people like to know everything that is going on with their illness, whereas others may want to know what is most important but not necessarily all the details. How much do you want to know? Is there anyone else you would like me to talk to about your condition?"
- "What do you call your illness and what do you think caused it?"
- "Do any traditional healers advise you about your health?"

Practitioners should avoid stereotyping based on religious or cultural background. Each person is an individual and may or may not adhere to certain cultural beliefs or practices common in his or her culture. Asking patients about their beliefs and way of life is the best way to be sure you know how their values may impact their care [37].

The following sections provide a glimpse of the beliefs and practices of the major world religions. This overview is meant only to give a very simple, brief summary of the general ideology of each religion. By no means are all of the rites or beliefs described practiced by all members of each religion; likewise, not all religious rites or beliefs are discussed for each religion. As always, individualized assessment is encouraged.

### **Judaism**

Judaism emerged in the Southern Levant (an area in the Middle East) in about 2000 B.C.E. [136]. There are approximately 13 million Jewish people in the world—6 million in North America, 4.3 million in Asia, and 2.5 million in Europe [137]. Jewish descent is traced through the maternal line, but the choice to practice Judaism is made by the individual. In Jewish tradition, the Torah is believed to be the word of God and the ultimate authority.

There are three tenets of Judaism. The first tenet is monotheism; there is one God who created the universe and continues to rule [138]. The second tenet is that the Jews were chosen to receive the law of God (Yahweh) and to serve as role models for humankind [138]. The third tenet refers to the covenant, which is a contractual agreement between God and the Jewish people. According to the agreement, they will be rewarded if they obey God and keep his commandments; failing to do so would result in divine retribution. Also, they believe that studying the Torah and faithfulness to God and his commandments may hasten the arrival of the Messiah [136; 138].

Jewish law focuses on dietary practices, the Sabbath, and annual holidays or festivals. Observing the dietary laws is called keeping kosher. One's home is considered the table of the Lord, and therefore certain animals considered unclean (e.g., pork, shellfish) are not to be eaten. However, animals with split hooves and animals that chew their cud are acceptable. Acceptable animals must be slaughtered correctly, must have the blood drained from them, and must not be served with dairy products. Those who adhere to kosher laws have separate sets of dishes and utensils for preparing and serving meat, dairy products, and Passover meals [138; 139]. Passover, Rosh Hashanah, and Yom Kippur are major festivals observed by members of the faith.

### **Christianity**

Christianity emerged in the 1st century C.E. It is the largest religion in North America, and there are approximately 2 billion followers worldwide [136]. There are three major divisions in Christianity: Roman Catholicism, Eastern Orthodoxy, and Protestantism [136; 138]. Christianity is based on the life and teachings of Jesus Christ, and followers believe that salvation and eternal life can be obtained through their belief in Jesus [137]. The concept of the Trinity is also basic to Christian belief. Although God is perceived as one, God is also expressed in three roles: Father (Creator), Son (Redeemer), and the Holy Spirit (Sustainer) [138; 139].

Baptism and the Eucharist or Holy Communion are the primary sacraments celebrated in most Christian churches [138]. Baptism symbolizes the forgiveness of sins, new life, and initiation into the Christian church. During the baptism, persons are either immersed in water or water is sprinkled or poured over them. Eucharist or Holy Communion is a ritual meal in which bread and wine are taken in remembrance of the body and blood of Jesus that was broken and shed at the cross [136]. Major Christian holidays include Easter (commemorating the death and resurrection of Jesus Christ) and Christmas (celebrating the birth of Jesus).

Christians consider the Bible to be the word of God. It is composed of 66 to 81 separate books (depending on denomination). Christians hold various perspectives on the nature, purpose, and approaches to the interpretation of the Bible.

## Islam

Islam is the fastest-growing religion in the United States and throughout the world [140]. Members of Islam are called Muslims, and approximately 3.45 million live in the United States [140]. Islam began in Arabia around 570–632 C.E. and was founded by the prophet Muhammad. It is a monotheistic religion whose followers believe there is one God and that Muhammad was his last Prophet. They believe the Qur'an (or Koran) is the literal word of God (or Allah in Arabic) that was revealed to Muhammad and mediated by Gabriel, the angel of revelation [138]. Arabic is the language used in Islamic prayer/liturgy [137]. Major festivals or holidays include Al-Hijra, Milad un Nabi, Ramadan, Eid al-Fitr, Eid al-Adha, Day of Ashura, and Laylatul Qadr.

Most Muslims are of one of two denominations: Sunni and Shia. While various denominations may have slightly different beliefs or translations, Islam has six major doctrines. The first is the belief in divine unity, or tawhid [136; 138]. The second is the belief in angels as agents of God. Angels have many functions, such as carrying messages to prophets and watching over and keeping track of people. The third is a belief in prophecy as revealed in the Qur'an. The fourth involves belief in scripture (Qur'an), and the fifth is the belief in Judgment Day and life after death [136; 138]. On the Last Day (or final judgment), both the living and the dead will be judged. The faithful will be rewarded, and the unfaithful will be cast into hell. Finally, the sixth doctrine is the Divine Decree and Predestination. It suggests that Allah has already determined who will receive eternal salvation [136; 138].

The Five Pillars are the core beliefs and practices of Islam. The first is the Shahada (profession of faith)—the belief that there is no god but Allah, and Muhammad is his messenger [136]. The second pillar is the Salat (ritual prayer). Muslims pray facing Mecca five times every day: at dawn, noon, mid-afternoon, sunset, and evening [138]. The prayers are usually performed on a rug or mat specifically for this purpose. Zakat (almsgiving) is the third pillar of Islam. Muslims are expected to donate a certain portion of their income to community members in need [138]. Sawm (or fasting) is the fourth pillar of Islam. During the daylight hours of Ramadan, healthy adult Muslims are expected to abstain from food, drink, and sexual relations. This is a time of reflecting, renewing faith, and being grateful for everything Allah has given [138]. The fifth pillar of Islam is Hajj (pilgrimage). After 16 years of age, every Muslim in good health and whose finances permit is expected to visit the holy city of Mecca, located in present-day Saudi Arabia.

## Hinduism

Hinduism is one of the world's oldest religions, dating back to about 1500 B.C.E. [138]. Unlike other major religions, it was not founded by a single person but was born of many religious beliefs and philosophies [138]. Hinduism originated in India, and today it is the third-largest religion in the world. There are approximately 1.1 billion adherents worldwide and

2.3 million adherents in the United States [141]. Hinduism is a polytheistic religion with three major deities: Shiva, Vishnu, and Brahma [138]. There are many sacred texts in Hinduism, including The Ramayana, an epic tale of Lord Rama's victory over the 10-headed demon Ravana, and The Mahabharata, the world's longest epic poem that is an historical account of the birth of Hinduism along with a code of ethics for the faithful [136]. Major Hindu festivals include Makar Sankranti, Holi, Diwali, Mahashivratri, Vasant Panchami, Rama Navami, and Janmashtami/Krishna Jayanti.

Two concepts are central to Hinduism: karma and reincarnation. Karma refers to the spiritual principle of cause and effect. In short, people's circumstances are the result of present and past-life actions of good or evil [136]. Hindus also believe in the continuous cycle of life, death, and rebirth (reincarnation) that continues until the soul "transcends all pain and pleasure and release itself from all fears and attachments" [138]. This state is called samsara or transmigration [138].

The Hindu temple is a cultural center where people come to sing, read sacred texts, and perform rituals [136]. The chanting of mantra called pathas is a traditional Hindu practice and is believed to have transformative power. Puja or daily worship is an important aspect of Hinduism. It entails the offering of food, incense, flowers, fruits, ashes, and other articles to an image of a deity [138]. Tirthas refer to pilgrimage sites and holy places in Hinduism [138].

## Buddhism

There are approximately 3 million Buddhists in the United States and about 488 million worldwide [141]. Buddhism was founded in northeastern India by Siddhartha Gautam, whose name was later changed to the Buddha or Enlightened One. At 29 years of age, the Buddha sought knowledge from several forest yogis and learned meditation techniques. After six years, Buddhists believe Gautama found enlightenment while meditating under a Bodhi tree and was released from the cycle of rebirths [138]. He began promoting the idea of a middle path that focused on purity of thought and deed. Buddha believed awareness was the path to overcoming death [136]. He did not want to be worshiped as a god or savior. Instead, he believed his role was to help people find their path to freedom and enlightenment.

The Four Noble Truths and the Eightfold Path are essential to understanding Buddhism. The Four Noble Truths have been identified as the first teaching given by Buddha [137]:

- There is suffering in life.
- Human desire is the cause of suffering.
- The end of human suffering is possible.
- The Eightfold Path is how one achieves nirvana.

Collectively, the Four Noble Truths explain why humans suffer and how to overcome suffering. Within the Four Noble Truths is found the Eightfold Path. Wangu describes the Eightfold

Path as consisting of the right opinion, right intentions, right speech, right conduct, right livelihood, right effort, right mindfulness, and right concentration [138]. These eight paths are grouped into three key elements of Buddhist practice: morality, wisdom, and concentration [138].

Buddhists engage in rituals such as chanting and placing flowers, candles, and incense before an image of Buddha. Buddhists celebrate many holidays and festivals, most of which commemorate important events in the life of the Buddha. Every year, Buddhists celebrate Vesak, a festival that commemorates Buddha's birth, enlightenment, and death. During each quarter of the moon, followers of Buddhism participate in a ceremony called Uposatha [136]. This observance allows Buddhists to renew their commitment to their teachings. Buddhist New Year is a time for reflection of past lives and identifying and rectifying mistakes [136].

### Confucianism

Confucianism is described as a way of life, philosophy, religion, or ethical code by which to live [138]. It was developed from the teachings of Confucius, who was born around 551 B.C.E. [138]. These teachings focus on good conduct, wisdom, and proper social relationships. Confucius has had a great influence on Chinese culture. Although temples were built to honor him, he is not perceived as a god. The temples are used for public ceremonies only and not as places of worship [138].

Confucianism advocates eight key concepts. The first is Jen, which translates as love, human-heartedness, and goodness [138]. The second concept is Chun-tzu, which refers to a state of centeredness whereby one exhibits Confucians' values effortlessly and without the need for self-monitoring. The third concept is Li, or a sense of order in one's life that coincides with social convention. The fourth concept is Te, or the appropriate use of power by leaders and authority figures. The fifth concept is Wen, which refers to the cultural arts (e.g., music, drama, poetry) that help to maintain unity in society [138]. The remaining concepts are Chi (the wisdom of proper action), Hsin (integrity), and Yi (righteousness or justice).

### Taoism

Taoism (pronounced DOW-ism) is a Chinese philosophy and religion dating back to the fourth century B.C.E. [136]. Tao means "the way," and it has no founder or central figures. Taoists do not worship a god. Instead, they focus on coming into harmony with Tao, the cosmic energy that blows through everything. Taoism emphasizes what is natural and going with the flow of life. Today, there are about 20 million Taoists, and most followers live in China, Taiwan, or Southeast Asia [136].

Meditation is an important practice, and the goal of meditation is to come into harmony with the universe [136]. The philosophy is found in a text, the *Tao-te-Ching (Classic Way and Its Power)*, dating back to the third century B.C.E. and attributed to Lao Tzu [138].

### Shintoism

Shintoism began during prehistoric times on the Japanese islands [138]. Today, Shinto is the religion of Japan, and it has approximately 112 million followers; more than 75% of them follow Buddhism as well [138]. Like Taoism, Shinto has no founder or central figure. It teaches that all things in the world are imbued with a spirit (*kami*). Therefore, Shinto followers revere nature in all forms [138].

Most of the deities associated with Shinto are related to nature, such as the sky, earth, heavenly bodies, and storms [136]. However, deities are not different from humans, because everything is imbued with spirit. Everything is connected, including rocks, trees, dust, water, animals, and humans [138].

Shinto has no fixed doctrine and no scripture or sacred text. However, ancient prayers are passed down via oral tradition. Shinto followers worship primarily individually rather than in groups, and followers engage in purification rituals (e.g., handwashing) [138]. Worship occurs outside the shrine, and worshipers usually bring offerings of food or coins for the spirit (*kami*). These offerings are not given as sacrifices but as signs of gratitude [138]. Some followers write prayers on slips of paper and leave them nearby.

### New Age Spirituality

The New Age movement became popular in Western society in the 1970s [142]. The precise definition of the term differs among scholars largely due to its highly eclectic range of spiritual beliefs and practices [142; 143]. The movement takes many shapes and is continually changing. However, there are some common features that distinguish it from other religions, such as followers who [136]:

- Look forward to a society that reunites the wisdom of both science and religion
- Adopt holistic and alternative healing methods
- Embrace a wide array of traditional and nontraditional spiritual beliefs and practices
- Accept the existence of a universal energy that undergirds and permeates all of existence

Adherents believe healing can occur when individuals connect with this universal energy and learn to use it. This energy has been called by many names by different cultures, including *chi* (Chinese), *ki* (Japanese), *prana* (Sanskrit), *mana* (Pacific Islander), or the use of self as a final authority [136].

### GENDER

Gender identity is a vital aspect of a person's experience of the world and of themselves. It also impacts the ways in which the world perceives and treats individuals, with a clear effect on the effective provision of health and mental health care. This section will focus on persons presenting as cisgender male or female; special considerations for those who are transgender, non-binary, or gender nonconforming will be explored in the next section.

An increasing amount of research is supporting a relationship between men's risk for disease and death and male gender identity, and the traditional male role has been shown to conflict with the fostering of healthy behaviors [62; 63]. Male gender identity is related to a tendency to take risks, and the predilection for risky behavior begins in boyhood [63; 64; 65]. In addition, boys are taught that they should be self-reliant and independent and should control their emotions, and societal norms for both boys and men dictate that they maintain a strong image by denying pain and weakness [62; 64; 65].

Issues related to male gender identity have several important implications for health. First, risky behavior is associated with increased morbidity and mortality. Second, the concept of masculinity leads to inadequate help- and information-seeking behavior and a reduced likelihood to engage in behavior to promote health [62; 64; 65]. These behaviors appear to be rooted in a decreased likelihood for men to perceive themselves as being ill or at risk for illness, injury, or death [62]. Third, male gender identity, coupled with lower rates of health literacy, creates special challenges for effectively communicating health messages to men [66; 67; 68]. Gender differences in health-related behaviors are consistent across racial/ethnic populations, although specific behaviors vary according to race/ethnicity [63].

Men's beliefs about masculinity and traditional male roles affect health communication, and healthcare practitioners should consider male-specific beliefs and perceptions when communicating with male patients. For example, because men tend to focus on present rather than future health, concepts of fear, wellness, and longevity often do not work well in health messages [69]. Instead, healthcare practitioners should focus more on "masculine" concepts, such as strength, safety, and performance, all of which tie into men's perceptions of their roles as providers and protectors.

Although men are more likely than women to lack a regular healthcare provider and to avoid seeking help or information, women are more likely to have a chronic condition requiring regular monitoring and are more likely to have forgone necessary health care due to the cost [70]. In general, women are disproportionately affected by stresses related to caregiving, and this can be a barrier to help-seeking. Caregiving has been socialized as a feminine role, and two out of every three caregivers in the United States are women, meaning they provide daily or regular support to children, adults, or people with chronic illnesses or disabilities [145]. Women who are caregivers have a greater risk for poor physical and mental health, including depression and anxiety.

Women are more likely than men to be diagnosed with a mental health disorder, and more than 20% of women in the United States experienced a mental health condition in the past year [146]. In addition to being disproportionately affected, mental health conditions, such as depression and bipolar

disorder, can manifest differently in or have different impacts on women than men. Much of the research into women's health has focused on the perinatal period, which limits our knowledge of how mental illness affects women's lives.

There is also some evidence that women's pain is less likely to be taken seriously and controlled than male patients. A series of four studies found a relative gender-pain exaggeration bias, wherein perceivers believe women, relative to men, to be emotionally dramatizing and therefore more likely to exaggerate versus downplay their pain [147]. This bias may lead perceivers to interpret women's, relative to men's, pain reports as overstatements, inauthentic, or dramatized.

Providing gender-sensitive care to women involves overcoming the limitations imposed by the dominant medical model in women's health. This requires theoretical bases that do not reduce women's health and illness experience into a disease. This philosophy incorporates explanations of health and empowers women to effectively and adequately deal with their situations. The major components incorporated into the development of sensitive care include:

- Gender is a central feature.
- Women's own voices and experiences are reflected.
- Diversities and complexities are incorporated into women's experiences.
- Theorists reflect about underlying androcentric and ethnocentric assumptions.
- Sociopolitical contexts and constraints of women's experiences are considered.
- Guidelines for practice with specific groups of women are provided.

## GENDER AND SEXUAL MINORITIES

The gender and sexual minority (GSM) population is a diverse group that can be defined as a subculture. It includes homosexual men, lesbian women, bisexual persons, transgender individuals, and those questioning their sexual identity, among others. The GSM population is diverse, representing all ages and all socioeconomic, ethnic, educational, and religious backgrounds. The population has been described as "hidden and invisible," "marginalized," and "stigmatized." As a result, the unique health and safety needs of the population have often been overlooked or ignored. Clear definitions of the concepts related to sexual identity will be helpful. The following is a glossary of terms used in discussions of this group [71; 72; 73; 74; 75; 76]:

**Asexual/aromantic:** An individual who does not experience sexual attraction. There is considerable diversity in individuals' desire (or lack thereof) for romantic or other relationships.

**Bisexual:** An adjective that refers to people who relate sexually and affectionately to both women and men.

**Coming-out process:** A process by which an individual, in the face of societal stigma, moves from denial to acknowledging his/her sexual orientation. Successful resolution leads to self-acceptance. Coming out is a lifelong process for lesbian, gay, bisexual, and transgender persons and their families and friends as they begin to tell others at work, in school, at church, and in their communities.

**Gay:** The umbrella term for GSM persons, although it most specifically refers to men who are attracted to and love men. It is equally acceptable and more accurate to refer to gay women as “lesbians.”

**Gender and sexual minorities (GSM):** A term meant to encompass lesbian, gay, bisexual, trans, queer/questioning, intersex/intergender, asexual/ally (LGBTQIA) people as well as less well-recognized groups, including aromantic, two-spirited, and gender-fluid persons.

**Heterosexism:** An institutional and societal reinforcement of heterosexuality as the privileged and powerful norm.

**Heterosexuality:** Erotic feelings, attitudes, values, attraction, arousal, and/or physical contact with partners of the opposite gender.

**Homophobia:** A negative attitude or fear of non-straight sexuality or GSM individuals. This may be internalized in the form of negative feelings toward oneself and self-hatred. Called “internalized homophobia,” it may be manifested by fear of discovery, denial, or discomfort with being LGBTQIA, low self-esteem, or aggression against other lesbians and gay men.

**Homosexuality:** The “persistent sexual and emotional attraction to members of one’s own gender” as part of the continuum of sexual expression. Typically not used to describe people.

**LGBTQIA:** An acronym used to refer to the lesbian, gay, bisexual, transgender/transsexual, queer/questioning, intersex/intergender, asexual/ally community. In some cases, the acronym may be shortened for ease of use or lengthened for inclusivity. Members of this group may also be referred to as gender and sexual minorities (GSM).

**Queer:** An umbrella term to describe persons with a spectrum of identities and orientations that are outside of the heteronormative standard.

**Sexual identity:** The inner sense of oneself as a sexual being, including how one identifies in terms of gender and sexual orientation.

**Sexual orientation:** An enduring emotional, romantic, sexual, and/or affectionate attraction to another person. Individuals may experience this attraction to someone of the same gender, the opposite gender, both genders, or gender nonconforming.

**Transgender:** An umbrella term describing a number of distinct gender positions and identities including: crossdressing, transsexual, nonbinary, and intersex.

One’s intrapersonal acceptance or rejection of societal stereotypes and prejudices, the acceptance of one’s self-identity as a sexual minority, and how much one affiliates with other members of the GSM community varies greatly among individuals [77]. Some authors stress the diversity within the GSM community by discussing “GSM populations” [78]. For example, it is understandable that a GSM population living in rural areas of the United States would have little in common with a GSM population living in urban areas or “gay-friendly” neighborhoods. Additionally, mental health experts have suggested that “GSM community” symbolizes a single group of individuals who express their sexuality differently than the majority of heterosexual individuals. However, many distinct communities have been identified, including lesbian, gay, bisexual, and transgender [79]. Each community is different from the other as well as different from the heterosexual community. A culturally competent healthcare provider should keep this diversity in mind so that vital differences among these smaller groups are not lost when thinking of the GSM population in general.

Commonalities exist among the GSM communities as well. For example, many adolescents, whether gay, lesbian, bisexual, transgender, or questioning their sexual identity, lack sexual minority role models to assist with successful psychosocial development [79].

The subtle and pervasive ways that discomfort with GSM individuals may be manifested have been examined and, in some instances, categorized as “cultural heterosexism,” which is characterized by the stigmatization in thinking and actions found in our nation’s cultural institutions, such as the educational and legal systems [80]. “Cultural heterosexism fosters individual antigay attitudes by providing a ready-made system of values and stereotypical beliefs that justify such prejudice as natural” [81]. Perhaps the paucity of information about the GSM community in basic professional education has been a reflection of cultural heterosexism. Writers, funding sources, and publishers have been exposed to the same cultural institutions for many years.

Individuals generally begin to absorb these institutional attitudes as children and may consequently develop “psychologic heterosexism,” which may also manifest as antigay prejudice. Many individuals, as children, have little contact with someone who is openly gay and, as a result, may not be able to associate homosexuality with an actual person. Instead, they may associate it with concepts such as “sin,” “sickness,” “predator,” “outsider,” or some other negative characteristic from which the individual wants to maintain distance [81]. Psychologic heterosexism involves (among other factors) considering sexual identity and determining that one does not want to think further about it. The direction of this thinking is undeniably negative, resulting in an environment that allows antigay hostility [81]. The impact of antigay prejudice on the physical and mental health of members of the LGBTQIA community and their families should not be underestimated [82; 83].

Sexual minority individuals also are not immune to societal attitudes and may internalize negative aspects of the antigay prejudice experience. Anxiety, depression, social withdrawal, and other reactions may result [2; 84]. While the study of psychologic heterosexism, both blatant and subtle, is in the early stages of research, it has had a measurable impact on the mental health of the GSM community [85; 86; 87; 88].

Examples of the range of manifestations of heterosexism and/or homophobia in our society are readily available. Without difficulty, each example presented here may be conceptualized as related to the emotional or physical health of a GSM individual or family member:

- A kindergarten student calls another child an LGBTQ+ slur but does not really know what he is saying.
- A teenage girl allows herself to become pregnant, “proving” her heterosexuality to herself, her family, and her friends.
- A parent worries that her 12-year-old daughter is still a “tomboy.”
- An office employee decides to place a photo of an old boyfriend in her office rather than a photo of her gender-nonconforming partner of five years.
- A college student buries himself in his studies in an effort to ignore his same-sex feelings and replace feelings of isolation.
- Two teenage girls, thought by peers to be transgender individuals, are assaulted and killed while sitting together in an automobile.
- A female patient is told by a healthcare provider that her haircut makes her look like a lesbian and is examined roughly.
- A gay man chooses not to reveal his sexual identity to his healthcare provider out of fear of a reduction or withdrawal of healthcare services.

The manifestations of heterosexism have inhibited our learning about the LGBTQIA population and its needs [78]. Gay patients have feared open discussion about their health needs because of potential negative reactions to their self-disclosure. Prejudice has impacted research efforts by limiting available funding [77]. All of these factors emphasize that the healthcare education system has failed to educate providers and researchers about the unique aspects of LGBTQIA health [83; 89].

### **Common Myths**

Many myths surround homosexuality; a few are outlined below. The origin of these myths may be better understood after examining the history of homosexuality as well as the attitudes toward human sexuality in general. The history of the development of societal norms related to homosexuality includes misconceptions developed during times when research was not available on which to build a scientific knowledge base [82; 90; 91; 92].

*Myth: Sexual orientation is a choice.*

**Fact:** No consensus exists among scientists about the reasons that an individual develops his/her sexual orientation. Some research has shown that the bodies and brains of gay men and women differ subtly in structure and function from their heterosexual counterparts; however, no findings have conclusively shown that sexual orientation is determined by any particular factor or set of factors. Many people confuse sexual orientation with sexual identity. The reader may consider reviewing the definitions of these terms when further considering this myth.

*Myth: Gay men and lesbians can be easily identified because they have distinctive characteristics.*

**Fact:** Most gay and lesbian individuals conform to the majority of society in the way they dress and act. Further, a person's appearance is not necessarily an indication of sexual or romantic interests.

*Myth: Gay individuals are child molesters.*

**Fact:** This is a very damaging and heterosexist position. According to experts in the field of sexual abuse, the vast majority of those who molest children are heterosexual. The average offender is a White heterosexual man whom the child knows.

*Myth: Gay people want to come into our schools and recruit our children to their “lifestyle.”*

**Fact:** Efforts to bring issues related to LGBTQIA history and rights into schools are not efforts to “convert,” just as education on European history is not an effort to glamorize or “convert” to European identity. The intent has been to teach a more complete history of the world and to prevent children from mistreating LGBTQIA individuals, who are often the subjects of harassment and physical attacks. There is no evidence that people could be “recruited” to a gay sexual orientation, even if someone wanted to do this.

### **AGE**

Elderly patients should be routinely screened for health and mental health conditions using tools specifically developed for this population, in spite of some practitioners' discomfort with asking questions about sensitive topics. These population-appropriate assessments may be included in other health screening tools [93].

Wellness and purpose have become important emphases when working with older adults [94]. In the past, aging was associated with disability, loss, decline, and a separation from occupational productivity. Although patient growth and positive change and development are values that practitioners embrace, the unconscious acceptance of societal myths and stereotypes of aging may prevent practitioners from promoting these values in elderly individuals [95].

### **Common Myths of Aging**

Society holds several myths about the elderly. Many of these myths may be easily disputed based on data from the U.S. Census and other studies.

*Myth: Most older adults live alone and are isolated.*

**Fact:** In 2018, 70% of men and 46% of women 65 years and older were married. An estimated 28% lived alone [96]. According to a survey conducted in 2009, 9 out of 10 individuals 65 years of age and older stated they talked to family and friends on a daily basis [97]. In 2016, an estimated 20% of the U.S. population lived in a household comprised of two adult generations or a grandparent or at least one other generation, compared with 12% in 1980 [97; 98]. This multigenerational household trend particularly affects those 65 years and older, with 21% of these individuals living in multigenerational households in 2016. This group was second only to individuals 25 to 29 years of age (33%) [98]. Several factors have contributed to this trend, including growing racial and ethnic diversity and adults getting married later [97; 98].

*Myth: Most older adults engage in very minimal productive activity.*

**Fact:** In 2016, 18.6% of persons 65 years and older were employed or actively looking for work, and this population represents approximately 8% of the total labor force in the United States [99]. The elderly are more engaged in self-employed activities than younger persons. In 2016, 16.4% of those 65 years of age and older were self-employed, compared with an average of 5.5% of those 16 years to 64 years of age [100].

*Myth: Life satisfaction is low among the elderly.*

**Fact:** Data from the Berkeley Older Generation Study indicate that many elders are quite satisfied with their life [101]. More than one-third (36%) of persons older than 59 years of age and 15% of those older than 79 years of age stated they were currently experiencing the best time in their lives. A 2009 survey found that 60% of individuals 65 years of age and older stated they were very happy. A 2012 survey found that 65% of individuals 65 years of age and older indicated that the past year of their life has been normal or better than normal, and more than 80% of respondents agreed with the statement, “I have a strong sense of purpose and passion about my life and my future” [102]. Most of the factors that predict happiness for the young, such as good health and financial stability, also apply to the elderly. Older adults tend to report higher levels of well-being in part due to the quality of their social relationships [103].

## PERSONS WITH MENTAL OR PHYSICAL DISABILITY

### *What health disparities are experienced by disabled persons?*

Americans with disabilities represent a large and heterogeneous segment of the population. The prevalence of disability varies by age group and definition. Based on the U.S. Census Bureau’s 2013 American Community Survey (ACS), which describes disability in terms of functional limitations, 12.6% of the civilian U.S. noninstitutionalized population has a disability, defined as difficulty in hearing or vision, cognitive function, ambulation, self-care, or independent living [104].

The U.S. Department of Education, which uses categorical disability labels, estimates that 13% of children and youth 3 to 21 years of age have a disability (defined as specific learning disabilities, speech or language impairments, intellectual disability, emotional disturbance, hearing impairments, orthopedic impairments, other health impairments, visual impairments, multiple disabilities, deafblindness, autism, traumatic brain injury, or developmental delay) [104].

People with disabilities experience many health disparities. Some documented disparities include poorer self-rated health; higher rates of obesity, smoking, and inactivity; fewer cancer screenings (particularly mammography and Pap tests); fewer breast-conserving surgeries when breast cancer is diagnosed; and higher rates of death from breast or lung cancer [104].

Disability cultural competence requires appreciation of social model precepts, which recognize patients’ rights to seek care that meets their expectations and values. The social model of disability has been characterized as centering disability as a social creation rather than an attribute of the patient [105]. As such, disability requires a social/political response in order to improve environmental factors affecting access and acceptance [105]. This involves adoption of person-first language, acknowledgement of social and environmental factors impacting persons abilities, and confronting disability-associated stigma.

## VETERANS

The effects of military service and deployment to military combat on the individual and the family system are wide-reaching. According to the U.S. Department of Defense, there were 3.5 million current military personnel in 2020 and 18.3 million veterans in 2017 [132; 133]. The Army has the largest number of active duty members, followed by the Navy, the Air Force, and the Marine Corps [132]. Military service presents its own set of risk and protective factors for a variety of mental health issues, including post-traumatic stress disorder (PTSD), traumatic brain injury (TBI), depression and suicide, substance abuse, and interpersonal violence. In particular, transitioning from combat back to home life can be particularly trying for veterans and their families.

As the number of military conflicts and deployments has increased since 2001, the need to identify and provide better treatment to veterans and their families has become a greater priority. The first step in providing optimal care is the identification of veterans and veteran families during initial assessments, with an acknowledgement that veterans may be any sex/gender and are present in all adult age groups [133].

Unfortunately, veterans and military families often do not voluntarily report their military service in healthcare appointments. In 2015, the American Medical Association updated its recommendations for social history taking to include military history and veteran status [134]. In addition, the American Academy of Nursing has designed the Have You Ever Served? Initiative to encourage health and mental health professionals to ask their patients about military service and



related areas of concern [135]. This program provides pocket cards, posters, and resource links for professionals working with veterans and their families. Recommended questions for intake include [135]:

- Have you or has someone close to you ever served in the military?
- When did you serve?
- Which branch?
- What did you do while you were in the military?
- Were you assigned to a hostile or combative area?
- Did you experience enemy fire, see combat, or witness casualties?
- Were you wounded, injured, or hospitalized?
- Did you participate in any experimental projects or tests?
- Were you exposed to noise, chemicals, gases, demolition of munitions, pesticides, or other hazardous substances?

### DIETARY CONSIDERATIONS

Cultural or personal beliefs can also impact the dietary needs of patients, which, in turn, can affect their health and adherence to prescribed treatments. For example, health issues related to fasting may arise among Buddhists, Hindus, Muslims, and some Christian patients, as well as persons of other faiths. This may particularly become an issue during extended fasts, such as the Muslim observance of Ramadan, which continues for one month [148]. Fasting is done during Ramadan as a spiritual exercise and is mandatory for all healthy adults. Those exempt from Ramadan fasting include children (prior to the onset of puberty); developmentally disabled individuals; the elderly; those who are acutely or chronically ill, for whom fasting would be detrimental to health; travelers who have journeyed more than approximately 50 miles; and pregnant, menstruating, or breastfeeding women [148]. Practitioners should advise all patients for whom fasting would prevent healing or adequate care (e.g., inability to take medication) to postpone or abstain from the ritual, if possible [148].

Another dietary consideration for some patients is whether medications contain animal-sourced ingredients. Vegetarians, vegans, Jewish people, Muslims, and others may need to know which products are from animal sources. Common examples of meds that contain ingredients from animals include:

- Desiccated thyroid from pig thyroid glands
- Heparin from pig intestines
- Pancreatic enzymes from pig pancreases
- Certain vaccines grown in eggs
- Conjugated estrogens from pregnant mares' urine

In addition, the gelatin used to make capsules and even some tablets and vaccines is often hydrolyzed collagen from animal tissues. Over-the-counter medications and supplements that may have animal-source ingredients include glucosamine (from shellfish), vitamin D3 (from lanolin, or sheep's wool), calcium (from oyster shells or bone meal), and omega-3 fatty acids (from fish oils).

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### PROMOTING CULTURALLY SENSITIVE COMMUNICATION

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Communication, the process of sending a message from one party to another, consists of both verbal and nonverbal components. Verbal and nonverbal communications are embedded within the culture of the parties disseminating the information and within the culture of the parties receiving the information. Communication is complex and multilayered because it involves unstated, implicit rules about a variety of factors, including physical distance between parties, tone of voice, acceptable topics of discussion, physical contact, and amount of eye contact [106]. Each of these variables is influenced by the perception of the level of formality/informality of the situation. Frequently, misunderstandings occur because the decoding and interpretation of these nonverbal cues are not accurate.

The verbal component of communication is just as complicated. Certainly, similarity in language shared by both parties enhances communication, but assuming that both parties in a conversation speak the same language, how the information is interpreted is still influenced by a host of factors. Linguists have posited that approximately 14,000 different meanings and interpretations can be extracted from the 500 most common English words [107]. Consequently, practitioners must be aware of the different communication styles held by diverse ethnic minority patients, as the clinical communication process is the primary vehicle by which problems and solutions are identified and conveyed [108].

Styles of communication can be classified from high- to low-context [109]. High-context cultures are those cultures that disseminate information relying on shared experience, implicit messages, nonverbal cues, and the relationship between the two parties [107; 110]. Members of these cultural groups tend to listen with their eyes and focus on how something was said or conveyed [106; 109]. On the other hand, low-context cultures rely on verbal communication or what is explicitly stated in the conversation [107]. Consequently, low-context communicators listen with their ears and focus on what is being said [106; 109; 110]. Western culture, including the United States, can be classified as a low-context culture. On the other hand, groups from collectivistic cultures, such as Asian/Pacific Islanders, Hispanics, Native Americans, and African Americans, are from high-context cultures [109].

Communicators from high-context cultures generally display the following characteristics [106; 107; 110; 111]:

- Use of indirect modes of communication
- Use of vague descriptions
- Less talk and less eye contact
- Interpersonal sensitivity
- Use of feelings to facilitate behavior
- Assumed recollection of shared experiences
- Reliance on nonverbal cues such as gestures, tone of voice, posture, voice level, rhythm of speaking, emotions, and pace and timing of speech
- Assimilation of the “whole” picture, including visual and auditory cues
- Emotional speech
- Use of silence
- Use of more formal language, emphasizing hierarchy between parties

On the other hand, low-context communicators can typically be described as [106; 107; 110]:

- Employing direct patterns of communication
- Using explicit descriptions and terms
- Assuming meanings are described explicitly
- Utilizing and relying minimally on nonverbal cues
- Speaking more and often raising their voices (more animated, dramatic)
- Often being impatient to get to the point of the discussion
- Using more informal language; less emphasis on hierarchy, more equality between parties (more friendly)
- Being more comfortable with fluidness and change
- Uncomfortable using long pauses and storytelling as a means of communicating

Understanding the distinctions between individuals who come from high- and low-context cultures can promote cultural sensitivity. However, it is vital that practitioners take heed of several words of caution. First, it is important not to assume that two individuals sharing the same culture (e.g., low-context culture) will automatically have a shared script for communicating. Second, it is important to not immediately classify an individual into a low- or high-context culture because of their ethnicity. A Chinese American man may not necessarily be a high-context communicator because he is Asian. A host of factors, such as level of acculturation, upbringing and socialization, education, and family immigration history, will all play a role in how one learns to communicate. Third, a major criticism of the discussion of low-/high-context cultures is that they reinforce dualism and ultimately oversimplify the complexities and nuances of communication [112].

Learning to communicate effectively also requires an understanding of how different conversational traits influence the communication process, or how information is conveyed and interpreted. Again, the goal of this section is not to simply dichotomize individuals’ conversational styles into categories, but rather to understand the factors that play a role in how someone makes a decision on how to communicate [106].

As long as there are two parties involved in a conversation, nonverbal communication is inevitable, and it becomes salient particularly when it is processed from one culture to another. Nonverbal communication is any behavior (including gestures, posture, eye contact, facial expressions, and body positions) that transcends verbal or written forms of communication [113]. Nonverbal communication can enhance or reinforce what is said verbally, and conversely, it can completely contradict the message communicated verbally. It can also end up replacing what was verbally communicated if both parties do not share a native language [114].

In Western culture, communication is more direct and eye contact is highly valued. When eye contact is not maintained, many Westerners assume that the party is hiding pertinent information. However, in some cultures, reducing eye contact is a sign of respect [108]. Conversely, patients may interpret direct and indirect gazes differently. For example, in one study, Japanese individuals tended to rate faces with a direct gaze as angry and less pleasant compared with Finnish participants [115].

The amount of social space or distance between two communicating parties is culturally charged as well. Depending upon the social context, Westerners tend to maintain a distance of about three feet, or an arm’s length, in conversations [107]. In a public setting, where both parties are engaged in a neutral, nonpersonal topic, Westerners will feel encroached upon and uncomfortable if an individual maintains a closer conversational distance. However, in other cultures, such as Latino and Middle Eastern, a closer distance would be the norm [107]. Chung recommends that in a clinical setting the practitioner allow patients to set the tone and social distance [116]. The practitioner can sit first and permit the patient to select where they want to sit.

Cross-cultural communication is by no means simple, and there is no set of rules to merely abide by. Instead, promoting culturally sensitive communication is an art that requires practitioners to self-reflect, be self-aware, and be willing to learn. Therefore, as practitioners become skilled in noticing nonverbal behaviors and how they relate to their own behaviors and emotions, they will be more able to understand their own level of discomfort and comprehend behavior from a cultural perspective [106].

## CULTURALLY SENSITIVE ASSESSMENT GUIDELINES

Practitioners may be categorized as either disease-centric or patient-centric [117]. Disease-centered practitioners are concerned with sign/symptom observation and, ultimately, diagnosis. On the other hand, patient-centered practitioners focus more on the patient's experience of the illness, subjective descriptions, and personal beliefs [117]. Patient-centered practice involves culturally sensitive assessment. It allows practitioners to move assessment and practice away from a pathology-oriented model and instead acknowledge the complex transactions of the individual's movement within, among, and between various systems [118].

Practitioners who engage in culturally sensitive assessment nonjudgementally obtain information related to the patient's cultural beliefs, overall perspective, and specific health beliefs [119]. They also allow the patient to control the timing [120].

The goal is to avoid the tendency to misinterpret health concerns of ethnic minority patients. Panos and Panos have developed a qualitative culturally sensitive assessment process that focuses on several domains [119]. Each domain includes several questions a practitioner may address in order to ensure that he or she is providing culturally responsive care.

Alternatively, Kleinman suggests that the practitioner ask the patient what he or she thinks is the nature of the problem [121]. He highlights the following types of questions that may be posed to the patient [121]:

- Why has the illness/problem affected you?
- Why has the illness had its onset now?
- What course do you think the illness will follow?
- How does the illness affect you?
- What do you think is the best or appropriate treatment? What treatment do you want?
- What do you fear most about the illness and its treatment?

Similar to Kleinman's culturally sensitive assessment questions, Galanti has proposed the 4 Cs of Culture [122]:

- What do you call the problem?
- What do you think caused it?
- How do you cope with the problem?
- What questions or concerns do you have about the problem or treatment?

Pachter proposed a dynamic model that involves several tiers and transactions, similar to Panos and Panos' model [123]. The first component of Pachter's model calls for the practitioner to take responsibility for cultural awareness and knowledge. The professional must be willing to acknowledge that they do not possess enough or adequate knowledge in health beliefs and practices among the different ethnic and cultural groups they come in contact with. Reading and becoming familiar with medical anthropology is a good first step.

The second component emphasizes the need for specifically tailored assessment [123]. Pachter advocates the notion that there is tremendous diversity within groups. Often, there are many intersecting variables, such as level of acculturation, age at immigration, educational level, and socioeconomic status, that influence health ideologies. Finally, the third component involves a negotiation process between the patient and the professional [123]. The negotiation consists of a dialogue that involves a genuine respect of beliefs. The professional might recommend a combination of alternative and Western treatments.

Beckerman and Corbett further recommend that recently immigrated families be assessed for [124]:

- Coping and adaptation strengths
- Issues of loss and adaptation
- The structure of the family in terms of boundaries and hierarchies after immigration
- Specific emotional needs
- Acculturative stress and conflict for each family member

Practitioners should seek to understand the sociopolitical context of the origin country [125]. A migration narrative is also recommended, whereby an individual provides a story of their migration history. Asking about how long the family has been in the United States, who immigrated first, who was left behind, and what support networks are lacking gives the practitioner an overview of the individual's present situation [126]. The theme of loss is very important to explore. Types of losses may include family and friends left behind, social status, social identity, financial resources, and familiarity [126]. For refugees and newly immigrated individuals and families, assessment of basic needs (e.g., food, housing, transportation) is necessary [125].

Culturally sensitive assessment involves a dynamic framework whereby the practitioner engages in a continual process of questioning. Practitioners should work to recognize that there are a host of factors that contribute to patients' multiple identities (e.g., race, gender, socioeconomic status, religion) [127].

## CREATING A WELCOMING AND SAFE ENVIRONMENT

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### *What is the basis of establishing a safe and welcoming environment for all patients?*

Improving access to care can be facilitated, in part, by providing a welcoming environment. The basis of establishing a safe and welcoming environment for all patients is security, which begins with inclusive practice and good clinician-patient rapport. Shared respect is critical to a patient's feeling of psychological well-being. Security can also be fostered by a positive and safe physical setting. For patients who are acutely ill, both the illness experience and treatment process can produce trauma. This is particularly true if involuntary detainment or hospitalization is necessary, but exposure to other individuals' narratives of experienced trauma or observing atypical behaviors from individuals presenting as violent, disorganized, or harmful to themselves can also be traumatic. As such, care environments should be controlled in a way to minimize traumatic stress responses. Providers should keep this in mind when structuring the environment (e.g., lighting, arrangement of space), creating processes (e.g., layout of appointments or care systems, forms), and providing staff guidance (e.g., non-verbal communication, intonation, communication patterns). During each encounter, the patient's perception of safety is impacted by caretakers and ancillary staff.

Experts recommend the adoption and posting of a nondiscrimination policy that signals to both healthcare providers and patients that all persons will be treated with dignity and respect [128]. Also, checklists and records should include options for the patient defining their race/ethnicity, preferred language, gender expression, and pronouns; this can help to better capture information about patients and be a sign of acceptance to that person. If appropriate, providers should admit their lack of experience with patient subgroups and seek guidance from patients regarding their expectations of the visit.

Front office staff should avoid discriminatory language and behaviors. For example, staff should avoid using gender-based pronouns, both on the phone and in person. Instead of asking, "How may I help you, sir?" the staff person could simply ask, "How may I help you?" Offices that utilize electronic health records should have a system to track and record the gender, name, and pronoun of all patients. This can be accomplished by standardizing the notes field to document a preferred name and pronoun for all patients [129]. Some persons who identify as non-binary (i.e., neither or both genders) may prefer that plural pronouns (e.g., they) be used.

Questions should be framed in ways that do not make assumptions about a patient's culture, gender identity, sexual orientation, or behavior. Language should be inclusive, allowing the patient to decide when and what to disclose. Assurance of confidentiality should be stressed to the patient to allow for a more open discussion, and confidentiality should be ensured if a patient is being referred to a different healthcare provider. Asking open-ended questions can be helpful during a history and physical.

The FACT acronym may be helpful for healthcare providers. Providers should:

- Focus on those health issues for which the individual seeks care
- Avoid intrusive behavior
- Consider people as individuals
- Treat individuals according to their gender

Training office staff to increase their knowledge and sensitivity toward persons will also help facilitate a positive experience for patients.

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## CONCLUSION

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Culture serves as a lens through which patients and practitioners filter their experiences and perceptions. Patients will bring their unique life stories and concerns to the practitioner, and their cultural values and belief systems will inevitably shape how the problem is defined and their beliefs about what is effective in solving the problem. However, the cultural backgrounds and values of patients are not necessarily scripts that define behavior, and when practitioners view culture as a strength and not a pathology, practitioners will be able to more effectively join with patients to mobilize change.

Customer Information and Evaluation are located on pages 79–80.

# Chronic Cough in Adults

## **Audience**

This course is designed for nurses, physicians, and physician assistants/associates involved in the care of patients with chronic cough.

## **Course Objective**

Chronic cough is difficult to effectively assess and treat, leading to extended periods before diagnosis and significant negative impact on patients' quality of life. The purpose of this course is to provide clinicians with the knowledge and skills necessary to identify and treat patients with chronic cough, regardless of underlying etiology, in accordance with clinical guidelines.

## **Learning Objectives**

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

1. Describe the background and terminology related to chronic cough.
2. Compare and contrast available cough severity measures.
3. Outline the epidemiology of chronic cough and underlying etiologies.
4. Evaluate the impact of chronic cough on various dimensions of patients' lives.
5. Discuss the natural history and course of chronic cough.
6. Describe the pathophysiology of chronic cough.
7. Outline components of the initial evaluation of patients with chronic cough.
8. Identify potential underlying etiologies of chronic cough as well as appropriate management approaches for these conditions.
9. Analyze available treatment modalities for chronic cough of various underlying causes, including upper respiratory, lower respiratory, and reflux-associated cough.
10. Identify appropriate modalities for the treatment of refractory chronic cough, including pharmacotherapy, nonpharmacologic approaches, and investigational agents.

## **Faculty**

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

## **Faculty Disclosure**

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

## **Division Planner**

Mary Franks, MSN, APRN, FNP-C

## **Senior Director of Development and Academic Affairs**

Sarah Campbell

## **Division Planner/Director Disclosure**

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

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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.



EVIDENCE-BASED  
PRACTICE  
RECOMMENDATION

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

## INTRODUCTION

Chronic cough, or cough lasting longer than eight weeks, is a debilitating disease that can result in patients coughing hundreds to thousands of times every day. This physically exhausting and socially isolating condition can persist for years or decades, degrade the quality of life in nearly every domain, and result in numerous medical and psychosocial consequences, yet its adverse impact on patients is often overlooked or underappreciated by clinicians. While acute cough is typically transient and self-limited, chronic cough often poses a diagnostic and therapeutic challenge; both non-treatment and over-treatment with ineffective medication are common [1; 2]. Cough that persists despite investigation and treatment is especially vexing for patients and clinicians [3].

## BACKGROUND

### *How are acute, subacute, and chronic cough defined?*

The anatomic, diagnostic protocol (ADP) established in the late 1970s that chronic cough in patients with negative chest x-ray findings is a symptom of asthma, postnasal drip, or acid reflux. Later refined to asthma, nonasthmatic eosinophilic bronchitis, upper airway cough syndrome, and GERD, it was

CHRONIC COUGH TERMINOLOGY	
Term	Definition
Acute cough	Cough lasting less than 3 weeks
Subacute cough	Cough lasting 3 to 8 weeks
Chronic cough	Cough lasting more than 8 weeks
Refractory chronic cough	Cough that persists despite guideline-based treatment of the presumed underlying cause(s)
Unexplained chronic cough	No diagnosable cause of cough is found despite extensive investigation for common and uncommon causes
Allotussia	Cough triggered by innocuous stimuli (e.g., laughing, talking, changes in ambient temperature)
Hypertussia	Exaggerated coughing triggered by mildly tussive stimuli (e.g., strong odors, second-hand cigarette smoke)
Urge to cough (laryngeal paresthesia)	A distinct, often debilitating sensation of irritation or “itch” in the throat or chest that precede cough and is not satiated by coughing
Cough reflex hypersensitivity	The cardinal feature of cough hypersensitivity syndrome
Cough hypersensitivity syndrome	Disorder characterized by cough triggered by mildly tussive or innocuous stimuli, with features of allotussia, hypertussia, and/or laryngeal paresthesia
<i>Source: [5; 9; 26]</i>	

Table 1

believed that treating these underlying etiologies led to a favorable outcome in 90% of patients with chronic cough [4; 5; 6].

However, a large proportion of patients with these conditions do not have chronic cough [7]. Moreover, in many patients, cough persists despite treatment of its presumed cause (referred to as refractory chronic cough) or an underlying cause cannot be identified (referred to as unexplained chronic cough) [8]. This suggested that additional pathophysiological processes were involved [7].

In 2014, the European Respiratory Society (ERS) introduced cough hypersensitivity syndrome, defining chronic cough as a distinct clinical entity [9]. The 2020 ERS clinical practice guideline for chronic cough was pivotal in establishing cough hypersensitivity syndrome, influencing subsequent national and international chronic cough guidelines [10; 11; 12; 13].

In 2016, the “treatable traits approach” was introduced to improve the outcomes of pulmonary patients with complex clinical syndromes (e.g., asthma and COPD) and variable treatment responses by moving beyond practice guidelines directed at diagnostic categories as a single disease entity, to identify and treat relevant phenotypic and endotypic “traits” instead [14; 15; 16]. The treatable traits approach gained rapid acceptance in pulmonary medicine and endorsement in chronic cough guidelines [5; 17; 18].

Cough performs an essential physiological function, mediated by cough reflex pathways in the airways and brain. In some individuals, irritation or inflammation of vagal afferent nerves in the airway leads to cough reflex hypersensitivity, the cardinal feature of cough hypersensitivity syndrome, periph-

eral and central sensitization, and clinical manifestations of allotussia, hypertussia, and/or laryngeal paresthesia (**Table 1**) [3; 19; 20]. The demographic, pathophysiological, and clinical similarities between cough hypersensitivity syndrome and chronic neuropathic pain are numerous. Chronic pain research has substantially informed how chronic cough and cough hypersensitivity syndrome are understood; both are disorders of sensory processing [4; 21; 22].

Sensitization of cough pathways may persist long after resolution of the inciting acute or subacute event. These chronic coughs will remain unexplained by diagnostic workups that do not consider cough hypersensitivity. Cough hypersensitivity syndrome may improve with the targeted intervention of other treatable traits. If chronic cough persists, the patient has refractory chronic cough [5].

Refractory and unexplained chronic cough are diagnoses of exclusion. A thorough, systematic clinical workup is required so that non-obvious and obvious causes of chronic coughing can be identified. The treatable traits approach may significantly expand clinically important intervention targets. After a diagnosis of refractory/unexplained chronic cough is made, therapeutic attention shifts to downregulating the hypersensitive cough reflex [5].

Maturation in research and practice has led to novel and emerging therapeutic options for patients with refractory chronic cough. Randomized controlled trials of existing centrally acting agents have identified the efficacy of low-dose morphine and gabapentin [10; 23; 24]. The development of P2X3 receptor antagonists, a novel peripherally acting drug class, has led to the

approval of gefapixant for the treatment of refractory chronic cough in the European Union, Japan, and Switzerland, with U.S. Food and Drug Administration (FDA) advisory committee review believed imminent as of 2024 [25]. In a given patient, refractory/unexplained chronic cough may primarily involve peripheral mechanisms, central mechanisms, or both, and no tool is available for predicting therapeutic response to peripherally or centrally acting antitussive agents.

As of 2024, there are no FDA-approved treatments for chronic cough or for refractory chronic cough. When chronic cough persists after potential underlying causes are identified and treated according to current practice guidelines (e.g., for chronic cough related to nonasthmatic eosinophilic bronchitis or GERD), all therapeutic options for refractory chronic cough are prescribed off-label.

Important knowledge advances in this rapidly evolving field are not reaching healthcare professionals in the United States because chronic cough guidelines published for domestic consumption have become outdated. From this course, clinicians will gain current information on chronic cough and refractory/unexplained chronic cough, including the pathophysiology, differential diagnosis, and clinical management, essential for healthcare professionals in primary care, respiratory medicine, and ear/nose/throat (ENT) settings.

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## COUGH SEVERITY MEASURES

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### *What benefits do patient-reported outcome measures have over objective measures?*

Patients with chronic cough experience cough-related physical, psychological, and social burdens, which can result from different aspects of cough severity, including cough frequency, cough intensity, disruption of daily activities due to cough, and cough-specific health-related quality of life. The severity and impact of chronic cough on physical, psychological, and social domains can be quantified through several validated objective and subjective measures [27].

Patient-reported outcome measures obtain a comprehensive understanding of the impact across these domains [27]. Patient-reported outcomes capture many issues that cannot be assessed effectively by objective measures and are also inexpensive, readily available, convenient, and easy to use for the patient [28]. A minimal clinically importance difference, the smallest change in an outcome that patients would perceive as important, is established for both objective and patient-reported outcome tools [29]. Cough measures mentioned throughout this course are summarized in **Table 2**. Cough frequencies of greater than 700 over an hour have been recorded [28].

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## EPIDEMIOLOGY

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### PREVALENCE

#### *What is the estimated prevalence of chronic cough among U.S. adults?*

Cough is a frequent reason for seeking outpatient medical attention in the United States, accounting for as many as 30 million clinical visits per year, up to 40% of which result in specialist referral [31].

Chronic cough has a prevalence among U.S. adults of roughly 10%, of whom 92% visited healthcare clinicians in the past six months [32]. Chronic cough is estimated to cost \$6.8 billion annually in the United States, and an estimated \$3.6 billion is spent annually on over-the-counter therapies [33]. The economic implications of chronic cough include the cost of outpatient visits, plus diagnostic workups, prescription medications to treat cough, and lost work and lost school productivity [1]. While inconsistent definitions prohibit direct comparisons of chronic cough prevalence between different countries or ethnicities, chronic cough appears to be more common in Europe, North America, and Australia than in Asian countries [32; 34].

In KNHANES, a nationally representative study of the Korean adult population, the point prevalence of acute (<3 weeks), subacute (3 to 8 weeks), and chronic (>8 weeks) cough was 2.5%, 0.8% and 2.6%, respectively. The modal durations of current cough were less than one week (31.1%), and more than one year (27.7%); this bimodal distribution reflects the different pathophysiology of acute and chronic cough [35].

### REFRACTORY AND UNEXPLAINED CHRONIC COUGH

Refractory chronic cough is seen in 20% to 59% of patients presenting to specialist cough clinics [36]. At Kaiser Permanente Southern California, 11,290 patients with specialist-diagnosed chronic cough were treated and followed for one year; 40.6% continued coughing despite etiological treatment by specialists (i.e., refractory chronic cough) [37].

Roughly 10% of patients with chronic cough lack an identifiable cause despite thorough evaluation (i.e., unexplained chronic cough), including 17% of patients with chronic cough in the Kaiser Permanente cohort [1; 37]. Of 43,453 patients receiving primary care for chronic cough in the UK, 31% had ongoing chronic cough in the absence of associated comorbidities (i.e., no causal explanation or unexplained chronic cough) [4].



COUGH MEASURES		
Name	Domains/Items, Rating and Minimal Clinically Importance Difference (MCID)	Comments
<b>Health-related quality of life patient-reported outcome tools</b>		
Leicester Cough Questionnaire (LCQ)	Seven-point Likert scale (1=all of the time; 7=none of the time); 19 items in 3 domains: physical, psychological, and social. Total score range: 3 (maximal impairment) to 21 (no quality-of-life impairment). MCID: 1.5 to 2.5 increase	The most widely used tool for assessing quality of life impact of chronic cough
Cough Quality of Life Questionnaire (CQLQ)	Four-point Likert scale (1=strongly disagree; 4=strongly agree); 28 items over 6 domains: physical and extreme physical complaints, psychosocial issues, emotional well-being, safety fears, and functional abilities. Total score range: 28 (no adverse effect of cough) to 112 (worst possible impact). MCID: 10.6 to 21.9	Contains more items on physical impact of chronic cough (e.g., fractured ribs, headaches, immune deficiency, tuberculosis)
Hull Airway Reflux Questionnaire (HARQ)	Six-point scale (0=no symptoms; 5=most severe) of 14 items that measure airway hypersensitivity in chronic cough. Total score range: 0 to 70 Normal is <14 MCID: 16	Also used as a diagnostic tool for airway reflux, and to assess unexplained respiratory symptoms
Cough Severity Diary (CSD)	11-point scale (0=never; 10=constantly) of 7 items on frequency; intensity; disruptiveness MCID $\geq 1.3$ total score, -1.4 to -1.1 domain scores	Captures the severity and impact of chronic cough. Developed in response to patient feedback.
<b>Objective assessment tools</b>		
VitaloJAK Cough monitor Leicester Cough Monitor (LCM)	Electronic cough recording monitors worn by patients to measure cough frequency, typically as coughs per hour over 24 hours MCID: $\geq 20\%$ to 30% decrease	Does not capture the episodic nature of chronic cough, a primary factor in patients' disease burden
<b>Subjective tools</b>		
Visual Analogue Scale (VAS)	Score range 0 (no cough) to 100 mm (worst cough ever) MCID: 30-mm reduction on the 100-mm cough severity VAS	—
Numerical Rating Scale (NRS)	Score range 0 (no cough) to 10 (worst cough ever)	
Source: [28; 29; 30]		

Table 2

## DISEASE BURDEN AND HEALTHCARE UTILIZATION

The Kaiser Permanente study examined the disease burden of chronic cough in comorbidities, medication use, and exacerbations [37]. Diagnoses included GERD (44%), hypertension (42%), allergic rhinitis (33%), chronic rhinitis (31.5%), asthma (31%), chronic sinusitis (24.4%), obesity (24%), upper airway cough syndrome (20.4%), depression (20%), and cough complications (19%). Nearly 40% of patients with unexplained chronic cough consulted at least two different specialist depart-

ments. In the previous three years, about half of the patients with emergency department visits (28.5%) or hospitalizations (10%) were for respiratory events [37]. Medications were respiratory: nasal corticosteroids (55%), short-acting b2-agonists (50.5%), inhaled corticosteroids long-acting b2-agonist (27%), inhaled corticosteroid monotherapy (24%), and leukotriene modifiers (18.6%); non-respiratory: antitussive codeine (59%), proton pump inhibitors (PPIs) (45%), antidepressants (26%), anxiolytics (15.5%), and gabapentinoids (14%); and other: systemic antibiotics (72.4%) and oral corticosteroids (47%).

Over one year, patients with emergency department visits (26%) and hospitalizations (12%) remained high; more than 50% were respiratory-related. Antitussive and psychotherapeutic drugs were dispensed at a frequency similar to the baseline year. The clinical and economic burden was especially high in patients with both respiratory disease and GERD, but chronic cough persistence (40.6%) was similar between subgroups [37].

A subsequent Kaiser Permanente study of patient-level burden used patient-related outcomes (average chronic cough 8 years) [38]. Mean scores were 11 on LCQ (maximum: 21), 33 on HARQ (normal:  $\leq 13$ ), and 57 on CQLQ (maximum: 112). Correlations were high between LCQ and HARQ (-0.65), LCQ and CQLQ (-0.80), and HARQ and CQLQ (0.69). Patients with chronic cough-related respiratory and gastrointestinal disorders were generally similar. Treatment responses were suboptimal. Women (compared with men) and non-White individuals (compared with White individuals) reported significantly worse cough severity and poorer LCQ, HARQ, and CQLQ scores.

The patient-reported burden of chronic cough was substantial, with long duration, high severity, poor health status, high degree of cough hypersensitivity, low quality of life, multiple cough triggers, and frequent laboratory testing, specialist care, and medications. The study provides strong evidence that patients with chronic cough exhibit frequent poor responses to medications and overall control [38].

The objective and patient-reported burden of chronic cough is substantial, particularly in women and non-White minorities, which markedly affects daily living with inadequate response to treatments.

### RISK FACTORS

Risk factors of chronic cough include smoking, female sex, older age, obesity, asthma, allergic rhinitis, rhinosinusitis, and angiotensin-converting enzyme (ACE) inhibitor use for hypertension treatment [34; 39].

In the United States, 18% of adults who smoke cigarettes have chronic coughs [39]. Cigarette smokers are three times more likely to report chronic cough than never-smokers and ex-smokers, and the cough is usually due to chronic bronchitis. However, most patients in cough specialist clinics are nonsmokers [19]. Among 1,000 patients evaluated at a cough center in the Bronx, 2.7% were active smokers and 27% former smokers [40]. Of 11,290 Kaiser Permanente patients with chronic cough, 65% were never-smokers and 2.3% were current smokers [37].

Age and sex underlie the burden and prevalence of chronic cough; more than 67% of patients presenting with chronic cough to specialist clinics are female, likely due to gender differences in cough reflex sensitivity [1; 19]. Cough reflex sensitivity was assessed in individuals from China, India, and northwest Europe. No differences between ethnic groups were found,

suggesting that racial variation in chronic cough prevalence may not reflect differences in cough reflex sensitivity and may be influenced by asthma, allergy, or environmental factors [34; 39; 41]. Women in all three ethnic groups demonstrated lower cough thresholds [41].

While chronic cough can occur at any age, the rate rises substantially in women who are 40 years of age or older and is highest in the 60 to 69 age group. The highest rates in men occur between 50 and 69 years of age [1]. In KNHANES, chronic cough increased significantly with age. The odds ratio of 2.20 suggests a substantial increase in chronic cough likelihood for individuals 65 years of age or older (compared with those 18 to 39 years of age). The associations with older age were independent of current smoking and comorbidities [35].

In separate longitudinal European population studies, chronic cough was associated with low educational level and lower socioeconomic status [34]. A systematic review found a significant association between low education level and risk of chronic cough [42].

In South Korea and China, higher male prevalence of chronic cough was attributed to differences in smoking habits and air pollution exposures, respectively [28]. Occupational irritants, such as fumes, gases, cleaning products or dust, may cause cough by triggering cough reflex or by inducing oxidative stress and eosinophilic inflammation, but the effect of such factors on chronic cough remains elusive. Air pollution is an important risk factor for chronic cough. Levels of fine particulate matter  $\leq 2.5$   $\mu\text{m}$  in diameter (or PM<sub>2.5</sub>) are higher in East Asian than in European or North American countries but the prevalence of chronic cough is lower, suggesting potential host-environment interactions in developing chronic cough [19].

Persistent cough is a class-wide adverse effect of ACE inhibitors, and the 5% to 35% prevalence is much higher in East Asian than in other populations. In genotype studies, the genetic polymorphisms ACE I/D and SLCO1B1 were related to ACE inhibitor-induced cough and were more common in East Asian populations, which may account for the ethnic differences and possibly predict risk of ACE inhibitor-induced cough [43].

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### PATIENT IMPACT OF CHRONIC COUGH

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Patients report numerous cough-related physical and psychosocial effects, most commonly fatigue, sleep disturbance, exhaustion, breathlessness, headache, dizziness, musculoskeletal pain, wheezing, impairment of speech, vomiting, excessive perspiration, self-consciousness, and interference with daily activities [28; 44]. These effects have a significant impact on patients' quality of life.

## PHYSICAL IMPACT

### *What physical complications are associated with chronic cough?*

During vigorous coughing, intrathoracic pressures may reach 300 mm Hg and expiratory velocities approach 500 miles per hour (mph) (85% of the speed of sound). These physical forces cause many of the cardiovascular, gastrointestinal, genitourinary, quality of life, musculoskeletal, neurologic, ophthalmologic, psychosocial, and respiratory complications of chronic cough, ranging from the relatively minor to life-threatening or even fatal. Comorbid illnesses or older age can magnify these effects [44; 45].

### **Surgical Complications and Hernia**

Surgical complications from uncontrolled coughing include extrusion (i.e., expulsion) of ocular contents during eye surgery, and wound dehiscence (i.e., splitting or bursting open) following cardiac or abdominal surgery. Similarly, severe coughing can cause inguinal, femoral, umbilical, lumbar, or abdominal wall hernia [45].

### **Fracture**

Cough-induced rib fractures, another painful and potentially serious complication of chronic cough, often involve multiple ribs, particularly ribs 5 through 7. The number of ribs fractured is associated with higher mortality rates, particularly in older patients who often have decreased bone density due to osteoporosis (also an adverse effect of long-term corticosteroid treatment). However, rib fractures can also occur in patients with normal bone density [44; 46].

### **Stress Urinary Incontinence**

Stress urinary incontinence, defined as the unintentional loss of urine during or following a bout of coughing or other physical activity, significantly contributes to quality-of-life disruption caused by chronic cough in women. Of 210 consecutive adult women evaluated at a cough center for chronic cough, 63.3% reported stress urinary incontinence induced by cough episodes; stress urinary incontinence developed after the onset of chronic cough and solely occurred during or after coughing in 92.5% and at least daily in 47.3%. For context, 3.5% of similarly aged women in the community experience stress urinary incontinence, while only 5% of men with chronic cough report stress urinary incontinence as an issue significantly impacting their quality of life [28; 47].

Surveys have reported lower rates of urinary incontinence in women with chronic cough, but most women will not volunteer a history of cough-induced stress urinary incontinence unless specifically asked. This may explain the higher prevalence in this study, because the establishment of trust between patient and physician may have encouraged sharing such information. After discussion ensues, patients are often relieved to learn this is a common problem faced by women with chronic cough [47].

## Cough Syncope

Cough-evoked syncope is a serious and potentially fatal consequence of coughing. Numerous reports of motor vehicle accidents resulting from cough syncope include the deaths of drivers and pedestrians. While the exact mechanism remains debated, the required generation of very high intrathoracic pressures likely explains the nearly uniform profile of patients with cough syncope as large male subjects with obstructive airway disease [48]. Cough syncope is considered relatively uncommon, although 10% of subjects with chronic cough in a community sample reported experiencing cough syncope [5; 49]. The mandatory loss of driver's license in some countries (e.g., the UK) has a major impact on employment prospects for these patients [28].

## PSYCHOSOCIAL AND QUALITY OF LIFE IMPACT

Chronic cough can interfere with all aspects of patients' lives, including daily living activities, social interactions, home management, recreational activities, and employment. Importantly, when triggers of coughing bouts are very difficult to avoid, the psychosocial impact can be substantial. Chronic cough has a negative impact on relationships, with spouses not being able to tolerate the cough as a key reason for patients' health-related dysfunction [28]. In a multinational European survey of 1,120 persons with chronic cough, most reported that coughing affected their quality of life (96%), disturbed their family and friends (94%), and affected activities they enjoyed (81%) [51].

The psychological effects associated with chronic cough are highly prevalent, with an impact on mental health comparable to that of stroke or Parkinson disease. Studies of patients with chronic cough have reported high rates of anxiety (33% to 52%) and depression (16% to 91%) [28].

Patients may avoid or be uncomfortable in social situations due to the embarrassment of coughing, its effects (e.g., stress urinary incontinence, retching), and/or the perception by others that they have a contagious condition or are a heavy smoker [28]. The COVID-19 pandemic increased the social stigma of persistent coughing due to its association with contagious respiratory diseases [50].

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## NATURAL HISTORY AND DISEASE COURSE

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### *What FEV1 findings are common in adult patients with chronic cough?*

Little is known about the natural history of cough hypersensitivity, but the available evidence suggests that patients often suffer from it for many years [4]. In a longitudinal study of patients with unexplained chronic cough, cough severity worsened (36%) or was unchanged (23%) over 7 to 10 years. Predictors of cough persistence or improvement could not be identified. Unexpectedly, longitudinal spirometry data

showed declines in forced expiratory volumes over one second (FEV1) that were well above population norms for similarly aged nonsmokers. The striking magnitude of decline argued against a chance finding. Around 10% of patients developed spirometric features of COPD [52].

The abnormally rapid decline in FEV1 and a significant minority of patients developing COPD raise the possibility that unexplained chronic cough is associated with a persistent damaging airway process and could be a risk factor for COPD [52]. A 2023 study confirmed that chronic cough is highly associated with FEV1 decline, regardless of COPD presence, while chronic cough in patients suffering from COPD is associated with lower FEV1, more dyspnea, worse health status, and is an independent risk factor for exacerbations of COPD possibly linked to altered transient receptor potential (TRP) channel function [53].

Cough is often the most bothersome and intractable symptom reported by patients with asthma, and the significant disease burden of chronic cough was described in a prospective cohort of 323 consecutive adult participants with asthma who received optimized asthma therapy. After 12 months, those with chronic cough had more airflow obstruction; worse asthma control and quality of life; increased airway inflammation; upper respiratory tract infection as a trigger; more psychological, rhinitis, and COPD comorbidities; greater work productivity loss and daily activity impairment; and increased exacerbations. These findings call for more attention to chronic cough in asthma [54].

In summary, chronic cough is related to an accelerated FEV1 decline over time, regardless of smoking history or COPD diagnosis, but the relationship between chronic cough and worse clinical outcomes lacks a clear pathophysiological explanation [55].

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## PATHOPHYSIOLOGY OF CHRONIC COUGH

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### NORMAL PHYSIOLOGY

#### The Cough Reflex

Cough is an innate reflex that protects the airways from foreign objects, clears excess secretions, and preserves airway patency. The cough reflex consists of peripheral airway receptors of afferent nerves, cough control centers in the central nervous system (CNS), and efferent nerves.

Cough occurs in three phases [31; 56]. The first is inspiratory, during which the glottis opens widely followed by rapid inhalation sufficient for generating enough air movement to be productive. The second phase is compression. This phase is characterized by the rapid closure of the glottic apparatus and contraction of abdominal and other respiratory muscles compresses the alveoli and bronchiole, increasing intratho-

racic pressure to greater than 300 mm Hg. The final phase is expiration, or the sudden opening of the epiglottis and vocal cords results in rapid, high-volume expiratory airflow that may exceed 500 mph in velocity. The force of this process loosens and expels mucous secretions from the airway wall, while the rapid airflow vibrates the larynx and pharynx, inducing the characteristic sounds of cough.

#### Vagal Afferents

The cough reflex is activated by vagal afferent A- $\delta$  and C fibers, sensory neurons originating from brainstem vagal ganglia that innervate the larynx and proximal airways. A- $\delta$  fibers are mechanoreceptors, activated by airway mucus, inhaled foreign bodies, and low pH (i.e., acidity). C-fibers are nociceptive chemoreceptors, activated by signaling molecules and mediators of inflammation or tissue damage within the airway [19; 25; 57; 58].

#### Neurobiological Processes

Complex neurobiological processes in the peripheral nervous system, brainstem, and higher cerebral cortex mediate coughing [59]. Receptors (e.g., P2X3 purinergic receptors, voltage-gated sodium channels [NaV], bradykinin receptors, and transient receptor potential [TRP] ion channels) and neuropeptides (e.g., substance P, calcitonin gene-related peptide [CGRP]) play important roles [60].

Noxious mechanochemical stimuli in the airways activate ligand-gated ion channels and G protein-coupled receptors on vagal nerve endings; NaV channels depolarize, propagating the signal up the vagus nerve to first-order synapses in brainstem nuclei. From there, the signal is relayed by second-order neurons to brainstem and spinal motor neurons to reflexively modify breathing; to third-order neurons of the primary somatosensory cortex where the unpleasant urge-to-cough sensation is mediated; and to higher-order cortical neurons that mediate conscious perception of cough [23; 60].

These ascending third-order pathways enable perception of airway irritation, and regulatory control of descending motor pathways that terminate in the brainstem and in spinal respiratory circuits [22; 61]. Under physiologic conditions, higher inhibitory brain processes permit the modification of coughing behavior, and the urge to cough may be suppressed [21].

Extrapulmonary airways (i.e., larynx, trachea, and mainstem bronchi) are also reflexogenic sites essential for preventing aspiration, inhalation of noxious chemicals, and accumulation of excessive mucus; all can induce reflex coughing with irritation of vagal afferent nerves [21].

Coughing is a reflex and a voluntary behavior with or without the sensation of an urge to cough. Reflex cough, behavioral cough, and the urge to cough (which precedes the motor act of coughing) are three separate entities, each dependent on their own neural processes [21; 22]. The relevance of these neurophysiological processes is apparent when considering the development of cough hypersensitivity syndrome [21].

## PATHOPHYSIOLOGY OF CHRONIC COUGH AND COUGH REFLEX HYPERSENSITIVITY

Chronic cough, unlike protective cough, is a pathologic state that no longer serves a physiologic role [60]. Excessive coughing is a consequence of increased activation of neuronal cough-mediating pathways due to [62; 63]:

- Excessive activation of airway vagal afferent terminals by chemical or mechanical irritants
- Neuroplastic changes in vagal afferent fibers
- Neuroplastic changes in the CNS

Nervous system plasticity, or malleability, dictates that excessive stimulation of peripheral nerve fibers can reshape their excitability through changes in receptor expression; synaptic transmission in the CNS is subsequently altered, further increasing the gain within the system [62].

Chronic cough is most associated with and traditionally considered a symptomatic byproduct of asthma, nonasthmatic eosinophilic bronchitis, upper airway cough syndrome, and/or GERD, but most patients with these chronic inflammatory diseases do not have chronic cough. Further, cough severity correlates poorly with cough-associated disease severity, and chronic cough can occur in the absence of these conditions as unexplained chronic cough or unexplained chronic cough [19; 20; 64]. This implies individual differences in cough reflex sensitivity and that hypersensitivity of airway sensory nerves may underlie chronic cough [65].

Cough hypersensitivity, defined as repeated episodes of coughing often in response to minimal or no discernible triggers, is common to all persons with chronic cough [66]. Extracellular adenosine triphosphate (ATP) may play a prominent role in cough hypersensitivity. During cellular injury or inflammation, cells release ATP to alert neighboring cells to damage. In respiratory conditions associated with chronic cough and airway inflammation, such as COPD and asthma, extracellular ATP may be elevated and sensitivity to ATP is heightened [33]. The NK-1 receptor and its ligand, substance P, may also be involved in inducing and maintaining cough hypersensitivity, both peripherally and centrally, either indirectly through inflammatory mediators or directly by stimulating sensory nerve fibers [33].

### Cough Hypersensitivity Syndrome

#### *What is the cardinal feature of cough hypersensitivity syndrome?*

Cough hypersensitivity syndrome frames chronic cough as a hypersensitivity disorder, akin to chronic pain. Sensitization of vagal afferents by upper or lower airway inflammation leads to increased cough sensitivity to normally anodyne stimuli, the cardinal feature of cough hypersensitivity syndrome [22; 58].

In chronic cough, as in chronic pain, peripheral sensitization is necessary but probably insufficient without central sensitization, which alters the efficacy of neurotransmission in the

brainstem and regulation of cough reflex-mediating brain pathways [21]. Patients with cough hypersensitivity or chronic pain have shown abnormal activity in the same midbrain areas that amplify incoming cough (or pain) signals [58; 67; 68].

Chronic pain research substantially informs the conceptual transformation in how chronic cough and refractory chronic cough are understood. Both disorders involve abnormal sensory processing. Taking inspiration from chronic pain, hypertussia describes abnormal excessive coughing in response to airway irritation. Allotussia describes coughing in response to innocuous stimuli. Laryngeal paresthesia describes noxious sensations in the throat or chest associated with an “urge to cough.” Peripheral and central sensitization describe processes that alter cough pathway function [62; 63].

### *Peripheral Sensitization*

Dysregulation of airway innervation contributes to chronic coughing and is considered the main driver of cough in refractory chronic cough [63].

In airway inflammation, vagal neuron sensitization and plasticity is shown by increased production of neuropeptides, upregulation of glutamate receptors and nociceptive ion channels (e.g., TRPV1), and lower thresholds for activating sensory-evoked cough responses. Neuropeptide upregulation occurs in airway sensory neurons where they are not normally expressed. These effects underlie hypertussia by expanding the cough-evoking stimuli field [21].

For example, bronchoscopic biopsies of patients with chronic cough demonstrated increases in airway epithelial nerve length and branching. The remodeling of these vagal C fibers may contribute to airway hypersensitivity through increased density of fiber terminals and enlargement of their receptive fields. The shearing forces of chronically coughing and/or the resultant release of inflammatory mediators (e.g., ATP) may explain the increased density of epithelial innervation [69].

Whether the primary stimulus for peripheral sensitization is cellular damage, mechanical stress, or nociceptor stimulation is unclear, as all three can trigger ATP release, activating P2X3 receptors [59].

### *Central Mechanisms*

While peripheral nervous system dysfunction is the most-described component of cough hypersensitivity, central dysfunction plays a fundamental role [70]. Patients with cough hypersensitivity attempting to voluntarily suppress coughing show reduced activity in dorsomedial prefrontal and anterior mid-cingulate cortices, suggesting diminished ability to inhibit cough reflex activation [66; 67; 71].

Patients with refractory chronic cough demonstrate structural and functional alterations in the left frontal brain regions, including lower gray matter volume and enhanced frontoparietal functional connectivity, which may underlie the higher cough scores, greater psychosocial impact, longer disease duration, and impaired cough inhibition in these patients [72].

Studies of chronic cough in asthma and nonasthmatic eosinophilic bronchitis identified increased neuronal sensitivity and subsequent central sensitization via mechanisms of inflammatory-mediated nociceptor sensitization and altered afferent nerve terminal excitability, phenotypic changes in vagal afferent neurons, and central neuroplasticity resulting from increased synaptic signaling from peripheral afferents [73].

The contribution of CNS mechanisms accounts for the efficacy of centrally acting medications (e.g., gabapentin and low-dose morphine) in patients with refractory chronic cough [58].

### Laryngeal Hypersensitivity

A study of refractory/unexplained chronic cough patients with cough hypersensitivity referred to a cough clinic suggests highly prevalent laryngeal dysfunction. The 12-month cohort of all referred patients showed high rates of cough hypersensitivity (100%), multiple cough triggers (75%), laryngeal paresthesias (95%), voice abnormalities (50%), upper airway dyspnea (25%), and laryngeal functional abnormalities on nasoendoscopy (73%). Given the frequent constellation of symptoms typifying laryngeal dysfunction and cough hypersensitivity, the authors suggest designating laryngeal hypersensitivity as a specific cough phenotype [74].

Many refractory chronic cough cases have a sensory neuropathic etiology in the hypopharynx and larynx, with laryngeal hypersensitivity a key mechanism [75]. Pharyngeal/laryngeal sensations (e.g., irritation, tickle, throat-clearing), frequently associated with upper airway cough syndrome and reflux cough, may represent sensory neuron dysfunction of vagal afferents in the upper airways and a phenotype of cough hypersensitivity syndrome. Dysphonia, dysphagia, dyspnea, and abnormalities of vocal fold motion on laryngoscopy may present with chronic cough as part of the pharyngeal/laryngeal nerve dysfunction seen in cough hypersensitivity syndrome [76].

### Autonomic Dysregulation

There is also evidence of broader autonomic nervous system dysregulation. Compared with healthy controls, patients with chronic cough report more frequent and severe autonomic symptoms in gastrointestinal, orthostatic intolerance, bladder, and pupillomotor domains, primarily in parasympathetically mediated systems, suggesting this population may suffer from dysautonomia. Whether this results from coughing, or if both the cough and dysfunction are part of wider vagal pathology, is unclear [70].

### SUMMARY

Functional changes in TRPV1, TRPA1, and P2X3 nerve channels and the development of peripheral and central sensitization are thought to turn cough from a defensive reflex into a cough hypersensitivity syndrome [77]. Hypersensitivity of the cough reflex and deterioration in central inhibition of the cough explain cough persistence [78].

Cough hypersensitivity syndrome is identified by symptoms of allotussia, hypertussia, and/or laryngeal paresthesia and may improve with the treatment of other treatable traits. If the chronic cough persists, the patient has refractory chronic cough [5].

Owing to nervous system plasticity, sensitization of cough pathways may persist long after resolution of the inciting event, such as acute viral airway infection. These chronic coughs will remain unexplained by diagnostic workups that do not consider cough hypersensitivity [5].

Currently, there are no available methods to identify susceptibility to nervous system plasticity and sensitization, objectively diagnose cough hypersensitivity syndrome, or predict treatable versus refractory chronic cough.



According to the European Respiratory Society, cough hypersensitivity through cell damage and inflammation underlies much of the increased cough seen in other pathologies. The different pathological processes in individual conditions contribute to the disease-specific heterogeneous etiology of cough in other lung disease.

(<https://erj.ersjournals.com/content/55/1/1901136>.  
Last accessed August 12, 2024.)

**Level of Evidence:** Expert Opinion/Consensus Statement

## INITIAL EVALUATION OF CHRONIC COUGH

When initially encountering a patient with chronic cough, the primary task is to perform a thorough evaluation that seeks potential underlying treatable causes of chronic cough and to treat the cause(s) according to current clinical practice guidelines [99]. These patients typically undergo extensive medical workup and treatment across multiple subspecialties without improvements in their symptoms, and clinicians should try to break the often-repetitive cycle of investigations, empirical treatment, and worry experienced by these patients [75]. The degree to which patients have been investigated varies, so basic tests may be required. Further investigations depend on the individual's presentation [5]. After a diagnosis of refractory chronic cough is made, the therapeutic focus shifts from identification and treatment of underlying causes to suppression of the hypersensitive cough reflex [99].

The initial evaluation (detailed history and physical examination) accomplishes the key tasks of identifying or ruling out a wide range of diseases underlying the chronic cough and identifying any danger signs that may indicate a diagnosis that needs urgent attention. Any positive findings should guide the initial management [8; 44].

## DEFINITIONS OF COUGH

To eliminate confusion on how to define cough, the American College of Chest Physicians (ACCP) and the ERS have standardized the definition of cough according to its duration [10; 100]. Consistently applying these guideline-established definitions is crucial [2].

Thus, the first step in evaluating cough is to determine its duration. This also helps to narrow the differential diagnosis based on the most common underlying causes [10; 100]:

- Acute (<3 weeks) cough:
  - Infectious etiologies, especially with viral causes
  - Exacerbations of chronic diseases (e.g., asthma, COPD)
  - Pneumonia
  - Environmental exposures
- Subacute (3 to 8 weeks) cough:
  - Postinfectious cough
  - Exacerbations of chronic diseases (e.g., asthma, COPD)
  - Upper airway cough syndrome
- Chronic (>8 weeks) cough:
  - Upper airway cough syndrome
  - Asthma
  - Nonasthmatic eosinophilic bronchitis
  - GERD

In chronic cough, allergies are considered secondary to upper airway cough syndrome or asthma.

When cough has lasted three or more weeks and is not postinfectious, some experts recommend not waiting for eight weeks to begin a chronic cough workup [6].

## PATIENT HISTORY

A detailed evaluation is performed and should include the following [2; 5; 6; 8; 10; 100]:

- Presenting symptoms or cough characteristics:
  - Duration
  - Productive or nonproductive

- Associated symptoms (e.g., rhinorrhea, nasal congestion, sneeze, fever, sputum production, hemoptysis, dyspnea, weight loss, dysphonia, dysphagia, peripheral edema)
- Prior episodes
- Preceding illnesses (e.g., recent viral infection)
- Clarify whether the patient is coughing, throat-clearing, or both.
- Medical history, including pulmonary and extrapulmonary (e.g., GERD, hypertension, allergic, immune) conditions
- Surgical history, especially involving cardiac, pulmonary, gastrointestinal, and otolaryngological organ systems
- Family history of atopic disease
- Exposure history
  - Tobacco and cannabis smoking or vaping (e.g., electronic cigarettes)
  - Occupational and environmental exposures
  - Recent travel
  - Country of origin
  - Potential sick contacts
- Review current medications for potential iatrogenic cause. Ask about current use of both prescribed and over-the-counter NSAIDs and aspirin.

It is important to always rule out culprit medications by assessing whether the patient is taking an ACE inhibitor antihypertensive, NSAID, sitagliptin, or any medication that may be suspected of inducing the cough. A dry persistent cough from ACE inhibitor use is caused by bradykinin, substance P, and prostaglandins that accumulate in the upper respiratory tract or lung when ACE is inhibited, enhancing the cough reflex. Stopping the drug typically resolves coughing within four weeks or improves it sufficiently for a diagnosis of iatrogenic cough. Switching to angiotensin II receptor blockers (ARBs) provides antihypertensive control without provoking coughing [6; 101].

## PHYSICAL EXAMINATION

The physical examination of a patient presenting with chronic should assess for nasal congestion, pharyngeal erythema, tonsillar swelling, hoarseness, stridor, wheeze (particularly focal wheeze), crackles, and other adventitious sounds.

## MANDATORY INITIAL TESTS

Initial diagnostic testing should include chest radiography (usually x-ray). Spirometry testing of pulmonary function is recommended pre- and post-bronchodilator to evaluate possible asthma or COPD.





The European Respiratory Society suggests that clinicians do not routinely perform a chest CT scan in patients with chronic cough who have normal chest radiograph and physical examination.

(<https://erj.ersjournals.com/content/55/1/1901136>. Last accessed August 12, 2024.)

**Strength of Recommendation/Level of Evidence:**  
Conditional recommendation, very low-quality evidence

## “RED FLAG” ASSESSMENT OF SERIOUS UNDERLYING CAUSES OF COUGH

### *What findings on the initial evaluation of chronic cough require further evaluation?*

In cough of any duration, the initial evaluation should identify any danger signs that may indicate a diagnosis requiring urgent attention. Important danger signs that will need further evaluation with chest x-ray and possibly laboratory testing and computed tomography (CT) include [44; 100]:

- Systemic symptoms (raises suspicion for chronic infection or rheumatic disease):
  - Fever
  - Night sweats
  - Weight loss
  - Peripheral edema with weight gain
- Hemoptysis, an indicator of infection (e.g., bronchiectasis, lung abscess, tuberculosis), cancer (e.g., lung, bronchus, or larynx), rheumatologic diseases, heart failure, or foreign body inhalation
- Prominent dyspnea, especially at rest or at night, a possible clue to airway obstruction or lung parenchymal disease
- Possible foreign-body inhalation (requires urgent bronchoscopy)
- Smoker older than 45 years of age with a new cough, change in cough, or co-occurring voice disturbance
- Hoarseness
- Trouble swallowing when eating or drinking
- Vomiting
- Recurrent pneumonia
- Abnormal respiratory exam and/or abnormal chest radiograph coinciding with duration of cough

## RECORDS REVIEW

If patients have undergone prior evaluations for upper airway cough syndrome, asthma, GERD, or nonasthmatic eosinophilic bronchitis, obtain and review these medical records, including laboratory values, diagnostic reports, and treatments

prescribed, to determine if these etiologies have been accurately assessed, diagnosed, and treated. Patients may not have been completely evaluated for these conditions yet diagnosed based on their response (or lack thereof) to empiric trials, which is important to ascertain [2].

## THE ANATOMIC DIAGNOSTIC PROTOCOL (ADP)

Even in current international guidelines that emphasize treatable traits, the anatomic diagnostic protocol (ADP) remains useful in the clinical workup of patients with chronic cough for identifying possible treatable conditions, while recognizing that treatment of the presumed cause(s) does not always improve the cough [19]. Consistent with the ADP, this section organizes chronic cough etiologies and management by their lower airway, upper airway, and gastroesophageal origin.

In nonsmoking, immunocompetent patients not taking an ACE inhibitor and with unremarkable chest radiography, cough lasting longer than eight weeks is considered a symptom of asthma, nonasthmatic eosinophilic bronchitis, upper airway cough syndrome, GERD, or any combination [6]. These four common causes to consider should be evaluated (**Table 3**).

The ADP has been modified to simplify the clinical workup by emphasizing empiric treatment trials for suspected, but not fully investigated or confirmed, disease [77]. According to the rationale, objective diagnostic methods for upper airway cough syndrome, asthma, nonasthmatic eosinophilic bronchitis, and GERD are technically demanding, sometimes difficult for patients, and require specialized instruments and personnel. Further, with GERD, discerning causal and temporal relationships between acid reflux and cough is difficult. Thus, sequential empirical therapy is frequently considered and is advised by some before embarking on extensive workup [39; 102]. Because symptom reduction is said to confirm a diagnosis, empiric treatment has been called a diagnostic-therapeutic trial [1].

## DIAGNOSTIC TESTS

If airway disease is suspected, the treatable traits approach is advocated to identify and optimize treatment of pulmonary, extrapulmonary, and behavioral traits (**Table 4**). Optimizing airway disease treatment is usually the key to managing cough in these patients. Cough hypersensitivity may be a trait in airway disease and require additional specific treatment [5].

Classic asthma, cough-variant asthma, and nonasthmatic eosinophilic bronchitis are clinical diagnoses with no clear-cut, absolute diagnostic test available to either rule asthma in or out as the cause of a patient's chronic cough [10]. In a stepwise diagnostic approach, initial abnormal lung function testing suggests classic asthma or COPD; normal testing is inclusive of cough-variant asthma, nonasthmatic eosinophilic bronchitis, or chronic bronchitis. Absence of bronchial hyperreactivity to methacholine challenge in patients with normal physical exam and spirometry findings suggests nonasthmatic eosinophilic bronchitis. Negative airway responsiveness can exclude cough-variant asthma. Abnormal spirometry contraindicates bronchial challenge testing [104].



EVALUATION OF COMMON CAUSES OF CHRONIC COUGH				
Evaluation	Common Causes			
	Asthma	NAEB	UACS	GERD
Spirometry	X			
Bronchodilator reversibility	X			
Bronchoprovocation challenge	X			
Allergy evaluation	X	X	X	
Sputum eosinophilia		X		
Blood eosinophilia		X		
Fractional exhaled nitric oxide (FeNO)		X		
Sinus imaging			X	
Nasopharyngoscopy			X	
Empiric treatment trials <sup>a</sup>	X	X	X	X
<b><sup>a</sup>Diagnostic/Therapeutic Trials</b>				
UACS	First-generation oral antihistamines Inhaled corticosteroids Inhaled ipratropium			
Asthma or NAEB	Inhaled corticosteroids Systemic (oral) corticosteroids Leukotriene receptor antagonist			
GERD	High-dose proton pump inhibitor (PPI) acid-suppression therapy Anti-reflux lifestyle measures Pro-kinetic agent: metoclopramide			
GERD = gastroesophageal reflux disease; NAEB = nonasthmatic eosinophilic bronchitis; UACS = upper airway cough syndrome.				
Source: [1; 82; 83; 100]				Table 3

### Lung Function Tests

Spirometry can reveal airflow obstruction, variability (>20%) in peak expiratory flow measurements, or an improvement in threshold testing (FEV1 >12%, improvement from baseline of >200 mL) in response to bronchodilators (b-2 agonists). Abnormal spirometry can be seen in patients with classic asthma and COPD, but not cough-variant asthma or nonasthmatic eosinophilic bronchitis [104].

#### Spirometry

An FEV1/forced vital capacity (FVC) ratio of <70% (or below the lower limit of normal, if available) is a positive test for obstructive airway disease (obstructive spirometry) [103].

#### Bronchodilator Reversibility Test

Bronchodilator reversibility testing is recommended in patients with obstructive spirometry (FEV1/FVC ratio <70%). Following short-acting beta-agonist bronchodilator administration, improvement in FEV1 of ≥12%, together with an increase in volume of ≥200 mL, is a positive test [103].

### Airway Inflammation Measures

Asthma is often, but not always, mediated by eosinophilic inflammation, and measurement of airway inflammation has clinical utility because eosinophilic airway inflammation is associated with favorable inhaled corticosteroid response. Fractional exhaled nitric oxide (FeNO) levels and peripheral blood eosinophil count indirectly estimate airway eosinophilia [5; 10; 84].

Significant (>3%) sputum eosinophilia is the criterion standard for eosinophilic inflammation, but sputum eosinophilia may not be routinely available. Blood eosinophil count is simple and readily available but has diurnal and seasonal variability so multiple assessments should be performed. A blood eosinophil count >0.3 cells/mcL may indicate eosinophilic airway inflammation.

FeNO is a surrogate marker of eosinophilic airway inflammation and inhaled corticosteroid response in classic asthma. FeNO has a relatively high specificity in predicting asthma among patients with chronic cough, but a cut-off level for diagnosis lacks consensus. Elevated FeNO levels (>40 ppb)

AIRWAY INVESTIGATIONS IN PATIENTS WITH CHRONIC COUGH		
Investigation	Description	Utility
<b>Lower Airway</b>		
Chest radiograph	Plain radiograph of the chest from anterior or posterior aspect (occasionally lateral view)	<b>Mandatory.</b> Abnormal findings should be pursued first as potential cause of chronic cough.
Spirometry	Maximal inhalation and exhalation into a spirometer measures forced expiratory volume in one second (FEV1) and forced vital capacity (FVC)	<b>Mandatory</b> test for airflow obstruction. FEV1 $\leq$ 80% or FEV1/FVC ratio $<$ 70% predicted for age and sex prompts reversibility testing.
Bronchodilator reversibility test	Pre- and post-bronchodilator spirometry in patients with obstructive airflow to measure change 10 to 15 minutes after SABA (e.g., albuterol)	Increase in FEV1 $\geq$ 12%, or $\geq$ 200 mL, after SABA indicates reversibility. Ideally, perform before starting asthma therapy.
Fractional exhaled nitric oxide (FeNO)	Measurement of nitric oxide levels in exhaled breath to indicate eosinophilic airway inflammation	Increased FeNO levels correlate with type 2 airway inflammation in asthma or nonasthmatic eosinophilic bronchitis. High FeNO ( $>$ 30 ppb) may predict corticosteroids response.
Induced airway sputum	Patient inhales nebulized hypertonic saline (3% to 5%), inducing sputum expectoration for differential cell count analysis.	The criterion standard assessment of eosinophilic airway, routinely used in cough clinics but not widely adopted
Bronchial challenge/provocation test	Patient inhales histamine or methacholine; a $\geq$ 20% drop in FEV1 confirms bronchial hyperresponsiveness (positive test).	Positive test with isolated cough and normal spirometry indicates an anti-asthma therapy trial. A negative test makes asthma improbable.
Chest computed tomography (CT)	Provides better resolution of lung parenchymal and mediastinal structures than chest x-ray	In productive cough, may identify early lung fibrosis or confirm bronchiectasis. Low utility in chronic cough with normal physical exam and chest x-ray.
Bronchoscopy (fiberoptic)	Allows direct visualization of the upper and lower airways and bronchoalveolar lavage to obtain specimens	<b>Mandatory</b> in all patients with suspected inhaled foreign body. Endobronchial appearance typically normal in chronic cough with normal chest x-ray.
<b>Upper Airway</b>		
Laryngoscopy (fiberoptic)	Allows direct inspection of laryngopharyngeal area including epiglottis and vocal cords	Typically unremarkable, but may reveal laryngopharyngeal reflux. Suspected laryngeal dysfunction prompts challenge laryngoscopy.
Sinus CT imaging	Visualizes the frontal, ethmoid, and maxillary sinuses and nasal passages	May provide evidence of sinus opacification or mucosal thickening. Unclear role in patients with chronic cough without nasal symptoms.
<b>Other</b>		
Peripheral blood eosinophil count	Measures absolute number or relative percentage of eosinophils in peripheral blood	May help predict corticosteroid response in respiratory diseases; utility in chronic cough not established.
ppb = parts per billion, SABA = short-acting beta-agonist.		
Source: [10; 19; 103]		Table 4

support a diagnosis of asthma with typical symptoms, but the usefulness in predicting inhaled corticosteroid response in chronic cough is uncertain [5].

A meta-analysis of studies in patients with chronic cough reported significantly higher inhaled corticosteroid response rates in high (>25 ppb) compared with low FeNO (87.4% vs. 46.3%) [105]. After three weeks of high-dose inhaled corticosteroids, the response rate (defined as a  $\geq 1.3$ -point increase in LCQ) was 68% in patients with high FeNO and no other apparent etiology; LCQ scores and FeNO significantly improved. However, improvements in cough were unrelated to changes in FeNO levels, challenging their direct mechanistic link [106]. Thus, an inhaled corticosteroid trial should be prompted with FeNO >25 ppb but avoided with FeNO <25 ppb unless other factors suggest eosinophilic airway disease [5]. Treatment decisions should not solely hinge on FeNO values [6].

### Airway Hyper-Reactivity Measures

In patients with negative physical examination and spirometry findings, bronchial challenge testing (e.g., methacholine) should be performed to confirm airway hyper-reactivity consistent with symptomatic asthma [84]. Bronchial challenge testing is recommended in patients with reactive airway diseases to help diagnosis of asthma and nonasthmatic eosinophilic bronchitis as a cause of chronic cough. A negative bronchial challenge test (defined as an FEV1 decrease of <20% at the highest methacholine challenge dose [10 mg/mL]) has a high negative predictive value of asthma as an etiological diagnosis in chronic cough [104].

Airway eosinophilic inflammation can be present in both asthma and nonasthmatic eosinophilic bronchitis but can be distinguished by a methacholine inhalational challenge (positive in asthma, negative in nonasthmatic eosinophilic bronchitis) because substantially more mast cells localize in the smooth muscle layer in asthma compared with nonasthmatic eosinophilic bronchitis [6].

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## IDENTIFICATION AND MANAGEMENT OF UNDERLYING ETIOLOGIES

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The concept that chronic cough is a disease in its own right has only recently gained acceptance. Different phenotypes of this condition are recognized (e.g., asthmatic cough, reflux cough), but the underlying pathology involves hypersensitivity of the vagus nerve and its central projections. The paradigm of asthma, GERD, and postnasal drip causing the symptom of chronic cough was promulgated from the 1980s onwards. However, after it became apparent that many patients suffering from chronic cough with a particular disease label (e.g., asthma, GERD) failed to respond to treatments for that condition, clinical practice guidance changed [79].

Systematic evaluation and treatment guidelines for chronic cough, based on the anatomic locations of receptors and afferent pathways in the cough reflex, first appeared in 1977 [80]. Using such an approach was estimated to determine the cause of chronic cough in 100% of patients, and the subsequent cause-specific treatment was reportedly almost always successful. Termed the ADP, this stepwise diagnostic approach involves a targeted patient history and physical examination to investigate the possible cause/s of their cough. This information is then used to initiate a stepwise treatment approach until resolution of the cough symptoms [77].

The ACCP recommended the ADP in their comprehensive clinical practice guideline on cough in 1998 and in 2006 [81; 82]. More recent ACCP guidelines evaluate ADP components and provide treatment recommendations on the major causes of cough, including chronic cough due to GERD in 2016, asthma and nonasthmatic eosinophilic bronchitis in 2020, stable chronic bronchitis in 2020, and unexplained/refractory chronic cough in 2016 [77; 83; 84; 85; 86].

However, the understanding of chronic cough has evolved beyond the ADP, especially since 2020 with incorporation of cough hypersensitivity and the treatable traits approach into clinical practice guidelines and endotyping of many cough-associated chronic inflammatory conditions. These knowledge advances are not efficiently reaching U.S. clinicians, because ACCP guidelines on chronic cough have not kept pace. While the ADP remains an important structure of the diagnostic workup for chronic cough patients, its assumptions have been supplanted in recent international chronic cough guidelines.

### THE “TREATABLE TRAITS” APPROACH IN CHRONIC AIRWAY DISEASES

#### *In the context of the treatable traits approach, how is a trait defined?*

In the late 19th century, Sir William Osler established the modern approach to the diagnosis and treatment of disease, based on the principal organ system where symptoms and signs manifest, with some biological correlates. The Oslerian paradigm of disease classification using diagnostic categories has been in use for more than 100 years, with substantial merit, but limitations of the diagnostic label approach have become evident [16].

As noted, in 2016, the treatable traits approach was introduced to pulmonary medicine to overcome the shortcomings of the diagnostic label approach, which does not consider the biological complexity of airway diseases, the distinct endotypes present in each patient, or common patterns of disease such as chronic cough [14; 17].

The treatable traits approach addresses the complexity of chronic airway diseases as heterogeneous, frequently overlapping, and often comorbid conditions. In clinical trials of patients with asthma and COPD, the treatable traits approach

led to significantly greater improvements in health-related quality of life and biological outcomes and reductions in primary care visits (compared with usual care) [16].

A trait is defined as clinically relevant, measurable, and treatable. These traits can be identified by their phenotypes and/or endotypes in pulmonary, extrapulmonary, and behavioral/environmental domains, and can coexist, interact, and change over time in the same patient. The treatable traits approach is agnostic to the traditional diagnostic labels of asthma or COPD and can be used in any patient with airway disease. The treatable traits approach often extends beyond the diagnostic label itself to find more treatment targets, especially in complex patients with suboptimal response to conventional guideline-based treatment [87; 88]. In other words, the treatable traits approach represents a transdiagnostic model.

In asthma, many extrapulmonary traits present as connected comorbidities, meaning they coexist with asthma and may share mechanisms. Extrapulmonary traits (e.g., chronic rhinosinusitis, GERD, anxiety, atopic dermatitis) are clinically relevant as they predict poor outcomes, confound the management of asthma, and are treatable themselves. Through multidimensional assessment of pulmonary, extrapulmonary, and behavioral/environmental domains, the treatable traits approach identifies and targets extrapulmonary traits with effective treatments, improving both asthma and the comorbidity [89].

In the 1970s, the ADP extended the Oslerian classification system to cough, addressing the three common causes (asthma, postnasal drip, reflux) arising from three different anatomical areas. Refined to four causes (asthma, nonasthmatic eosinophilic bronchitis, upper airway cough syndrome, and GERD), this approach benefitted many patients, but in 30% to 40% of these patients, the coughing continues or a presumed cause cannot be identified [16; 90]. In 2023, COPD was added to become a fifth common potential underlying cause of chronic cough [24].

Chronic cough is associated with airway and reflux diseases that are heterogeneous, frequently overlapping, and often comorbid, the same characteristics the treatable traits approach addresses [14; 17]. For instance, asthma is a clinical syndrome with varying phenotypes and endotypes, rather than a single disease entity. COPD is an umbrella term encompassing different respiratory conditions sharing airflow obstruction. Asthma is not always eosinophilic, and GERD is not necessarily acidic [15]. Despite its relatively recent appearance, the treatable traits paradigm is endorsed throughout pulmonary medicine and in post-2019 (international) clinical practice guidelines on chronic cough.

#### ENDOTYPES OF COUGH-RELATED CHRONIC INFLAMMATORY DISEASES

A phenotype is an observed characteristic resulting from interactions between genotype and environment. An endotype is a specific biological pathway that forms the basis of observable traits in the phenotype [56].

In the 2016 treatable traits paper, the authors broadly call for a shift away from the classical Oslerian top-to-bottom approach (i.e., from symptoms to mechanisms) to reclassifying airway diseases bottom-up, by linking causal molecular pathways (i.e., endotypes) to disease phenotypes (i.e., from molecules to symptoms) [14].

This has been unfolding in allergy and immunology, and these advances are highly relevant to pulmonary medicine and to chronic cough. For instance, the chronic inflammatory diseases of asthma, allergic rhinitis, chronic rhinosinusitis with or without nasal polyposis, eosinophilic esophagitis, and atopic dermatitis, are now defined by a constellation of symptoms that may result from different pathological mechanisms and not as homogeneous diseases [91].

The discovery of new endotypes in allergic and immune diseases has prompted the transition from symptom-focused disease descriptions to biomarkers and pathogenetic pathways—from phenotypes to endotypes [91]. The imperative for transitioning to endotypes is heightened by FDA approval of several biologicals that target specific inflammatory pathways important in disease pathophysiology [92]. These include the most common chronic cough-associated disorders.

Immune dysregulation has been endotyped as type 1, type 2, and type 3 responses. Asthma has been commonly dichotomized as type 2 and non-type 2. Type 2 inflammation is the best-characterized endotype [91; 93; 94; 95].

Type 2 inflammation involves eosinophils as the key players, which contribute to chronic allergic inflammation by producing cytokines, or interleukins (IL), with specific roles in the inflammatory pathway. IL-5 promotes eosinophil recruitment to sites of inflammation. IL-4 and IL-13 promote immunoglobulin E (IgE) production and immune cell trafficking to tissue, driving and sustaining the type 2 response, tissue damage, and chronic inflammation. IL-31 activates binding sites on sensory neurons, which release CGRP and nerve growth factor, causing neurogenic inflammation. In non-type 2 asthma, Th2 cells migrate to asthmatic bronchi and change their phenotype to produce T1 effector cytokines, such as interferon- $\gamma$  (IFN- $\gamma$ ) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), inducing bronchial epithelial apoptosis and remodeling. TNF- $\alpha$  promotes neutrophilic inflammation, which correlates with sputum TNF- $\alpha$  levels in patients with severe asthma. In type 3 inflammation, innate lymphoid cells type 3 (ILC3), T helper lymphocyte type 17 (Th17), and Th22 cells produce cytokines IL-17, IL-22, and IL-23. This mechanism is particularly relevant in the pathogenesis of chronic rhinosinusitis with nasal polyps and neutrophilic asthma [91; 93; 94; 95].

In 2023, the European Academy of Allergy and Clinical Immunology (EAACI) published an updated disease taxonomy with advances in biomarkers, pathogenetic and metabolic pathways, and pathogenic genetic variants. This expanded nomenclature characterizes the following types with relevance to chronic cough [91].

**Type V: Epithelial Barrier Defect**

The epithelial barrier defect and microbial dysbiosis lead to dysregulation of the immune response, including extensive activation and release of inflammatory cytokines, chemokines and inflammatory mediators (histamine, leukotrienes, reactive oxygen species). The sequence of events eventually leads to tissue damage in asthma, chronic allergic rhinitis, chronic rhinosinusitis, and chronic rhinosinusitis with nasal polyps.

**Type VI: Metabolic-Induced Immune Dysregulation**

Obesity is a distinguishing variable for clustering and classifying asthma subtypes, and the number of obese patients with asthma has risen dramatically with increasing obesity rates. The obese asthmatic, more likely to be female with adult-onset asthma and to become corticosteroid resistant, has a higher risk of being hospitalized and more frequently presents with severe disease. Higher body mass index (BMI) is associated with increased circulating inflammatory mediators, blood neutrophils, and eosinophils. An additive effect of asthma and obesity further increases inflammatory mediators and airway inflammation.

An asthma endotype introduced in 2020, IL-6-high asthma, is characterized by elevated plasma IL-6 levels, increased markers of systemic inflammation, metabolic dysfunction, and obesity [96].

**Type VII: Inflammatory Drug Reactions**

These idiosyncratic reactions include hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs) and phenotypes such as NSAIDs-exacerbated respiratory disease in patients with asthma and/or chronic rhinosinusitis ± nasal polyposis. NSAIDs-exacerbated respiratory disease is a chronic inflammatory condition characterized by the triad of asthma, recurrent nasal polyps and hypersensitivity to NSAIDs/aspirin. In the underlying mechanism, cyclooxygenase (COX)-1 inhibition releases eicosanoid mediators, causing bronchoconstriction, increased vascular permeability, mucus production and recruitment of inflammatory cells.

These advances in endotyping chronic inflammatory diseases associated with chronic cough have not yet appeared in practice guidelines on chronic cough, with the exception of eosinophilic airway inflammation, but this science is being translated into practice. For example, cough is the most troublesome symptom for patients with asthma. Older patients with asthma and chronic cough show worse clinical outcomes in asthma control, quality of life, and airway obstruction, and more frequent moderate-to-severe exacerbations, partly explained by the interaction of chronic coughing with aging [97]. Non-type 2 inflammation (e.g., increased neutrophils) is associated with cough in older patients with asthma with chronic cough. Interferon- $\gamma$  is a non-type 2 biomarker that enhances cough reflex sensitivity by inducing calcium influx in vagal sensory neurons and is associated with increased cough in patients with refractory chronic cough. Older patients with asthma show

increased levels of sputum IFN- $\gamma$ . Non-type 2 inflammation (i.e., neutrophils and IFN- $\gamma$ ) is also associated with reduced inhaled corticosteroid response [54; 97; 98].

**TREATMENT****CHRONIC AIRWAY INFLAMMATION**

Treatment of chronic airway inflammation includes inhaled corticosteroids, long-acting beta-agonists, long-acting muscarinic antagonists, leukotriene receptor antagonists, systemic corticosteroids, and biologicals. Confirmation that chronic cough is due to asthma (or another chronic cough-associated condition) requires a beneficial response to therapy for asthma, as patients with asthma can also have chronic cough due to non-asthmatic causes [44].

For chronic cough due to cough-variant asthma or nonasthmatic eosinophilic bronchitis, the ACCP recommends inhaled corticosteroids as first-line treatment [84]. With incomplete response, the inhaled corticosteroid dose should be escalated and adding a leukotriene receptor antagonist should be considered. Other causes of cough should be reconsidered as well. For cough-variant asthma, adding beta-agonists should be considered.

In patients with chronic cough in asthma, the first-line treatment is inhaled corticosteroid with or without long-acting beta-agonist [6]. A leukotriene receptor antagonist or long-acting muscarinic antagonist may be added in for those who do not fully respond to initial treatment. Whether biologics can treat chronic cough related to asthma has not been studied.



EVIDENCE-BASED  
PRACTICE  
RECOMMENDATION

In adult and adolescent patients with chronic cough due to non-asthmatic eosinophilic bronchitis (NAEB), we suggest inhaled corticosteroids as first-choice treatment.

([https://journal.chestnet.org/article/S0012-3692\(20\)30045-3/fulltext](https://journal.chestnet.org/article/S0012-3692(20)30045-3/fulltext). Last accessed August 12, 2024.)

**Strength of Recommendation/Level of Evidence: 2B**  
(Weak recommendation based on moderate-quality evidence)

When an offending allergen cannot be identified or avoided, chronic cough associated with nonasthmatic eosinophilic bronchitis should be treated with an inhaled corticosteroid. Second-line therapy calls for escalation of the inhaled corticosteroid dose; if response remains incomplete, the patient should be assessed for other causes of cough and a trial of leukotriene receptor antagonist initiated. Occasionally, systemic corticosteroids may be needed.

Tiotropium may be another therapeutic option. In 17 patients with chronic asthmatic cough refractory to inhaled corticosteroid/long-acting beta-agonist, four to eight weeks of tiotropium (5 mcg/day) significantly improved cough reflex sensitivity and cough severity in a subgroup of 11 patients [107]. These results were replicated in a randomized comparison to theophylline 400 mg/day over four weeks. Both drugs improved cough severity and cough-specific quality of life. Tiotropium decreased cough reflex sensitivity, which correlated with changes in cough severity, and higher baseline cough reflex sensitivity predicted greater tiotropium response. The authors conclude that tiotropium may modulate cough reflex sensitivity to alleviate chronic cough in asthma refractory to inhaled corticosteroid/long-acting beta-agonist [108].

### EMPIRIC TREATMENT APPROACH

Empiric treatment of chronic cough is systematically directed at the four most common causes of cough, starting with upper airway cough syndrome. In its 2006 guideline, the ACCP states that therapy should be given in sequential and additive steps, because more than one cause of cough may be present [82]. Initial empiric treatment should begin with an oral first-generation antihistamine/decongestant.

If chronic cough persists after treatment for upper airway cough syndrome, asthma as the possible cause should be worked up next. If spirometry does not indicate reversible airflow obstruction, bronchoprovocation testing is performed in the evaluation for asthma.

With the diagnoses of upper airway cough syndrome and asthma ruled out or treated without the elimination of cough, nonasthmatic eosinophilic bronchitis should be considered next, with a properly performed induced sputum test for eosinophils. In most patients with suspected cough due to asthma, a bronchoprovocation challenge should be performed and, if the result is positive, some combination of inhaled corticosteroids, inhaled beta-agonists, and/or oral leukotriene inhibitors should be administered.

In patients whose cough responds only partially or not at all to interventions for upper airway cough syndrome and asthma or nonasthmatic eosinophilic bronchitis, treatment for GERD should be instituted next. In patients with cough whose condition remains undiagnosed after all of these conditions has been worked up, referral to a cough specialist is indicated.

When the cause of chronic cough is identified or suspected, there are two options [26; 44; 57; 109]. The first is to pursue one diagnostic and treatment path at a time; with incomplete response of the cough to one line of therapy, adding therapy for the next most likely diagnosis is reasonable. The second option in patients with more than one suspected cause and a cough that is especially disruptive is to empirically treat or evaluate the likely causes simultaneously. After the cough resolves, treatments can be stopped sequentially, starting with the least likely to have been helpful, observing the patient for any return of cough.

### BEHAVIORAL TREATABLE TRAITS

Nonadherence and poor inhalation technique strongly influence outcomes in airway disease. Despite their critical importance, the proportion of patients with poor technique is high, unimproved over the past 40 years, and often unaddressed by clinicians. These behavioral treatable traits can be improved using strategies such as patient-centered communication, motivational interviewing, shared decision-making, and simplification of drug regimens; and should be assessed in every follow-up visit [110].

Smoking cessation improves cough by resolving chronic bronchitis. Nicotine suppresses the cough reflex, and nicotine withdrawal due to smoking cessation may enhance cough hypersensitivity; hence, patients may experience more coughing for a period after quitting. This can be attenuated and quit rates improved by using nicotine replacement [5].

### LOWER AIRWAY ETIOLOGIES OF CHRONIC COUGH AND MANAGEMENT

Lower airway diseases commonly associated with chronic cough are classic asthma, cough-variant asthma, nonasthmatic eosinophilic bronchitis, and COPD [20].

Chronic cough is a central feature that develops in diverse pulmonary pathologies, such as asthma (an inflammatory airway disease) and idiopathic pulmonary fibrosis (an alveolar fibrosing disease), highlighting the significant role of dysregulated cough pathways in lung disease phenotypes [60]. Chronic cough prevalences have been reported for asthma (8% to 58%), COPD (10% to 74%), bronchiectasis (82% to 98%), interstitial lung disease (50% to 89%) and sarcoidosis (3% to 64%); in all five diseases, patients demonstrate cough reflex hypersensitivity, a cardinal feature of cough hypersensitivity syndrome [111].

Presence of chronic cough generally predicts impaired health status and more severe respiratory disease and is associated with greater symptom burden and disease severity in asthma, COPD, bronchiectasis, and interstitial lung disease. It has also been linked to greater exacerbations in asthma and bronchiectasis and increased mortality and lung transplantation in idiopathic pulmonary fibrosis [111].

#### Asthma and Nonasthmatic Eosinophilic Bronchitis

Asthma is a complex, chronic airway inflammatory disease of bronchial hyper-responsiveness, intermittent airflow obstruction, and symptoms of wheeze and dyspnea that impacts 26 million people in the United States, results in approximately 10,000 deaths annually, incurs an estimated \$56 billion annually in medical care and lost productivity costs, and accounts for cough in 24% to 32% of adult nonsmokers with chronic cough [84; 112; 113]. Asthma prevalence has increased with rising obesity rates. Obesity often precedes an asthma diagnosis, making it an important modifiable risk factor (or treatable trait) [5; 113].

In atopic asthma, the most common type (affecting approximately 50% of adults with asthma), allergens trigger innate and adaptive immune activity, releasing inflammatory mediators such as histamine, prostaglandins, and leukotrienes that promote bronchoconstriction and cough [20; 114]. Classic asthma describes symptoms of wheezing, chest tightness, and dyspnea. In these patients, immune response to allergen exposure results in airway inflammation, airflow obstruction, and characteristic symptoms. Increased mucous secretions in narrowing airways induce cough [31; 112].

Cough-variant asthma, in contrast, presents with persistent cough as the primary or only symptom. Cough receptor density is highest in the proximal airways, decreasing as the airways get smaller. In cough-variant asthma, inflammation is primarily in the proximal airways, where cough is stimulated, and less so distally, where inflammation and narrowing cause wheezing and dyspnea in classic asthma [31; 56]. Some have suggested that asthma-variant cough is a more appropriate term than cough-variant asthma, given that cough hypersensitivity symptoms are the chief complaints, while asthmatic features act as triggers and treatable traits of chronic cough in these patients [115].

Nonasthmatic eosinophilic bronchitis was first described in 1989 as corticosteroid-responsive chronic cough in nonsmokers with airway eosinophilia, but without variable airway obstruction or bronchial hyper-responsiveness [116]. Nonasthmatic eosinophilic bronchitis accounts for 10% to 30% of specialist referrals for chronic cough, but nonasthmatic eosinophilic bronchitis prevalence is uncertain, as its diagnosis requires assessment of eosinophilic airway inflammation [44; 84; 117]. In nonasthmatic eosinophilic bronchitis, patients have chronic cough, no symptoms or evidence of variable airflow obstruction, sputum eosinophilia, and normal bronchial provocation tests [56; 117].

Chronic cough in asthma is mechanistically complex, involving IgE or non-IgE mediated eosinophilic airway (i.e., atopic or nonatopic) inflammation, abnormal neuromechanical properties of the lungs, and presence of cough reflex hypersensitivity independently of airway eosinophilia or bronchial hyper-responsiveness [20].

Nonasthmatic eosinophilic bronchitis and asthma share airway eosinophilia and similar basal membrane thickening, but inflammatory mast cells primarily infiltrate the superficial airway epithelium in nonasthmatic eosinophilic bronchitis versus airway smooth muscle in asthma. Along with lower IL-13 expression in nonasthmatic eosinophilic bronchitis, this partially explains bronchitis and cough with normal airway responsiveness in nonasthmatic eosinophilic bronchitis [116; 118]. Nonasthmatic eosinophilic bronchitis lacks the airway hyper-responsiveness of cough-variant asthma, but both share atopic features of eosinophilia and airway inflammation [109].

Eosinophilic airway inflammation in cough-variant asthma is linked to more severe disease. Cough-variant asthma may be a precursor of classic asthma, and both cough phenotypes can manifest overlapping symptoms, airway inflammation, and bronchial hyper-responsiveness [20]. Chronic dry cough, eosinophilic inflammation, and chronic airflow obstruction can present in both cough-variant asthma and nonasthmatic eosinophilic bronchitis [56].

### Chronic Obstructive Pulmonary Disease (COPD)

COPD comprises several lung diseases, including emphysema and chronic bronchitis, with persistent and usually progressive airflow limitation associated with an enhanced chronic inflammatory response in the airways and lungs. Exacerbations and comorbidities contribute to the overall severity, while airway and systemic inflammation in COPD is related to disease progression and mortality [119; 120].

In the United States, 14.2 million adults had diagnosed COPD in 2021, of whom 25% were never-smokers, and COPD accounted for 354,000 deaths in 2020 [121; 122]. Among patients with COPD, 70% experience persistent cough and many consider it extremely severe and impairing [64].

Chronic bronchitis describes productive cough on most days of the week for at least three months total duration in two successive years. Chronic obstructive bronchitis is chronic bronchitis with spirometric evidence of airflow obstruction. Chronic asthmatic bronchitis is a similar condition with chronic productive cough, wheezing, and partially reversible airflow obstruction mostly found in smokers with a history of asthma [123].

Emphysema is defined as the permanent enlargement and damage of the lung air sacs with destruction of the airspace walls, causing symptoms of breathlessness. Emphysema can exist without airflow obstruction but is more common in patients with moderate or severe airflow obstruction [119].

COPD manifests as productive cough with airflow limitation and occasional bronchial hyper-responsiveness [20]. COPD and asthma share symptoms of cough, wheeze, and difficulty breathing. The blurred distinction between chronic obstructive bronchitis and chronic asthmatic bronchitis is termed asthma-COPD overlap [123].

Cigarette smoking is the primary risk factor, but only 15% of smokers develop clinically apparent COPD. Smokers with pre-existing airway reactivity, even in the absence of clinical asthma, have greater risk of developing COPD. Inflammation in the large and small airways can persist after smoking cessation. The genetic disorder alpha-1 antitrypsin deficiency is an important cause of emphysema in nonsmokers and markedly increases susceptibility to COPD in smokers [120; 123].

### Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis is an interstitial lung disease, a group of pulmonary disorders characterized by inflammation and/or fibrosis of the lung parenchyma associated with progressive dyspnea frequently resulting in end-stage respiratory failure. Interstitial lung disease affects 650,000 people and causes 25,000 to 30,000 deaths per year in the United States [124].

Idiopathic pulmonary fibrosis, the most common interstitial lung disease accounting for 35% to 61% of all patients, is a chronic, progressive, invariably fatal fibrotic lung disease [111; 124]. Despite approvals of two antifibrotic therapies, the five-year survival rate remains 25%, far worse than many common cancers. Pharmacotherapies slow the disease progression, but none address the significant symptoms of chronic cough, fatigue, and dyspnea suffered by 85% to 95% of patients with idiopathic pulmonary fibrosis [125].

Chronic cough in idiopathic pulmonary fibrosis predicts disease progression and mortality, is as distressing as breathlessness for patients, and remains one of the most difficult symptoms to control [64; 125]. Among 1,447 patients with idiopathic pulmonary fibrosis cough, every 1-point decrease in LCQ score increased the risk of respiratory-related hospitalization by 6.5%, death by 7.4%, and lung transplantation by 8.7% over 12 months. Worse cough-specific quality of life independently associated with increased risk of respiratory hospitalization, death, and lung transplantation [126].

Two breakthrough studies demonstrated that low-dose morphine and nalbuphine can safely decrease coughing in idiopathic pulmonary fibrosis patients, as will be described later in this course.

### Bronchiectasis

Bronchiectasis is a heterogeneous disorder characterized by infection, airway inflammation, failure of mucociliary clearance, and airway structural damage. Absolute suppression of cough is not recommended because bronchiectasis is a suppurative condition with an increased risk of infection. However, much of the cough exceeds what is physiologically needed for sputum clearance and is thus maladaptive or pathological [111]. Cough is a central clinical feature of bronchiectasis that contributes to impaired health status and may be an early indicator of disease exacerbation, but it is almost never evaluated [64].

### UPPER AIRWAY ETIOLOGIES OF CHRONIC COUGH AND THEIR MANAGEMENT

In upper airway cough syndrome, diverse chronic infectious, inflammatory, or neurogenic upper airway diseases induce chronic cough [20; 127]. While upper airway cough syndrome lacks a uniform definition, its prevalence in chronic cough patients is probably comparable to other major causes like asthma and GERD; in some studies, it is the first or second leading cause [39; 127].

Rhinitis, comprising most chronic upper airway diseases in upper airway cough syndrome, has a lifetime prevalence up to 33% in the United States [6]. Nasal mucosa inflammation due to allergic or non-allergic cause leads to mucus secretion, sneezing, nasal pruritus, and postnasal drip that irritates the airways and stimulates coughing [31]. In chronic rhinitis, these symptoms persist at least three months, inducing nasal obstruction and increased nasal discharge [119].

Rhinitis has numerous phenotypes and the nomenclature is not straightforward (**Table 5**). Allergic rhinitis requires immunoglobulin E (IgE)-mediated sensitization to an allergen exposure [6]. Chronic cough in patients with allergic rhinitis is often related to undiagnosed asthma or nonspecific bronchial hyperreactivity. Bronchial biopsy studies of patients with allergic rhinitis without asthma have shown inflammatory cell infiltration and active structural remodeling of the lower airways similar to that of patients with asthma, thereby potentially contributing to cough in these patients [128].

Chronic nonallergic rhinitis syndromes include chronic nonallergic rhinitis, nonallergic rhinitis with eosinophilia syndrome (NARES), atrophic rhinitis, and drug-induced rhinitis; nonallergic rhinitis accounts for up to 80% of cases [129]. Nonallergic rhinitis phenotypes include [6]:

- Vasomotor
- Irritant
- Infectious
- GERD-associated
- Chronic rhinosinusitis with or without nasal polyposis

Rhinosinusitis is preferred to sinusitis because purulent sinus disease without similar rhinitis is rare [130].

Chronic rhinosinusitis is an inflammatory disease of the sinonasal mucosal lining secondary to infectious and allergic etiology, with symptoms of anosmia, nasal obstruction, thick nasal drainage, and facial pressure [92]. Retention of sinus secretions, the key event in chronic rhinosinusitis development, fosters infection and is caused by obstruction or narrowing of sinus ostia, mucociliary dysfunction, or altered mucus composition; 90% of sinus infections involve the maxillary sinus [119]. Cough, one of the important symptoms of chronic rhinosinusitis, occurs in 1% to 5% of U.S. adults [131].

Chronic rhinosinusitis with nasal polyposis, representing up to 20% of chronic rhinosinusitis cases, is more debilitating than the phenotype without nasal polyposis. Comorbidities in chronic rhinosinusitis with nasal polyps are asthma (55% to 56%), allergy (12% to 77%), and allergic rhinitis (17% to 76%). Asthma with nasal polyps is harder to control and more prone to severe exacerbations [92; 93].



## DISTINGUISHING CHARACTERISTICS OF RHINITIS PHENOTYPES

Rhinitis Phenotype	Primary Symptoms	Associated Features	More Responsive to	Less Responsive to
Allergic	Sneezing, nasal pruritis, clear rhinitis	Ocular itching, wheezing, atopic dermatitis	INCS, INAH, FGAH, SGAH, SCS, AIT	Decongestants, ABX
Nonallergic noninfectious	Intermittent congestion, clear rhinitis	Physical triggers (temperature changes, food, irritants)	INCA, INAH, INAC	FGAH, SGAH, SCS, AIT, ABX
GERD-associated	Postnasal drip, throat clearing	Epigastric pain, heartburn, dysphagia	GERD diet and lifestyle changes, INAC	FGAH, SGAH, INCS, INAH, SCS, ABX, AIT
Chronic rhinosinusitis with or without nasal polyposis	Anosmia/hyposmia, unremitting congestion, facial pain/pressure	Wheezing, NSAID hypersensitivity	SCS, biologics, intermittent INCS	FGAH, SGAH, INAH
Infectious	Acute onset, sinus pressure, nasal congestion with purulent discharge	Viral prodrome, episodic nature lasting <2 weeks	Saline nasal lavage, INAH, decongestants, INAC	FGAH, SGAH, INCS, SCS, ABX, AIT

ABX = antibiotics; AIT = allergen immunotherapy; FGAH = first-generation oral antihistamines; GERD = gastroesophageal reflux disease; INAC = intranasal anticholinergics; INAH = intranasal antihistamines; INCS = intranasal corticosteroids, SCS = systemic corticosteroids; SGAH = second-generation oral antihistamines.

Source: [6]

Table 5

Chronic cough pathogenesis in upper airway cough syndrome was previously tied to postnasal drip, because the nose and sinuses lack vagal sensory innervation. However, only a minority of patients with postnasal drip have chronic cough, some patients with upper airway cough syndrome do not have postnasal drip, and the pathophysiology is more complex [11; 127].

In chronic rhinitis and rhinosinusitis, inflammatory mediators are transmitted via glossopharyngeal and vagal receptors in the pharynx and larynx, and via afferent fibers of the trigeminal nerve, sensitizing the cough reflex centrally [11]. Direct irritation of nasolaryngeal mucosa and stimulation of vagal afferents by postnasal drip lead to hematogenous spread of inflammatory mediators and neurogenic or systemic communication between upper and lower airways, resulting in airway sensory nerve inflammation, cough reflex hypersensitivity, and chronic cough [10; 39].

Convergence of trigeminal and vagal afferents in central cough pathways provides a mechanistic/neuronal link between upper airway disease and the development of cough hypersensitivity [5]. In general, upper airway diseases lead to chronic cough only if the cough reflex becomes hypersensitive; therefore, they are generally considered a trigger rather than a cause of chronic cough [11].

In 2024, nonallergic rhinopathy was introduced to replace vasomotor rhinitis as the term describing 80% of the larger nonallergic rhinitis category, prompted by evidence that neuroinflammation and TRPV1 receptor activation play important roles, rather than blood vessels. TRPV1 also contributes to nasal hyper-reactivity in allergic rhinitis, an entity called mixed rhinitis. The management of nonallergic rhinitis requires the correct diagnosis; rhinopathy draws attention to the underlying neuro-immune endotype [129; 132].

Chronic cough is triggered in many patients with chronic upper airway disease (usually allergic rhinitis or chronic rhinosinusitis with or without nasal polyps) with common symptoms and signs of postnasal drip, compulsive throat-clearing, nasal stuffiness, globus feeling, headache/facial pain, loss of smell and taste, recurrent hoarseness, and cobblestone appearance of the pharyngeal mucosa on inspection [11]. The most commonly used tool is the SinoNasal Outcome Test (SNOT) [92].

With numerous symptoms and unclear diagnostic criteria, upper airway cough syndrome diagnosis has been based on first-generation oral antihistamine response, which may have central antitussive effects. Upper airway and other airway disease is frequent in patients with chronic cough, making it unclear whether coughing arises from upper or lower airways [5].

A large case series found allergic rhinitis, classic asthma, chronic rhinosinusitis, and nasal polyposis in 46%, 31%, 12%, and 9% of patients with chronic cough, respectively. The high predictive value for concomitant asthma in upper airway cough syndrome calls for investigating lower airway pathology in chronic cough of upper airway origin [20].

Rhinitis is a principal contributor to upper airway cough syndrome. The lengthy differential diagnosis of rhinitis in upper airway cough syndrome includes both allergic and nonallergic diseases; many patients have a combination of both or mixed rhinitis. Distinguishing these will increase treatment success and decrease the time before symptoms improve [6].

Radiological investigations may be useful and are guided by nasal symptoms. Incidental sinus changes may be present in up to 33% of CT and 67% of MRI scans. PPIs should not be used to treat upper airway symptoms [5].

Laryngeal dysfunction and hypersensitivity are common in chronic cough [5]. Consider treatment of laryngeal hypersensitivity as a symptom of cough hypersensitivity. Laryngitis often leads to chronic cough with voice changes (e.g., hoarseness, aphonia). Chronic cough is frequent in functional voice disorders, (e.g., muscle tension dysphonia) [11].

In vocal cord dysfunction, laryngeal hypersensitivity leads to persistent laryngospasm due to different triggering factors, manifesting as cough, wheeze, breathlessness, and voice disturbance. Coughing can be both a trigger and a symptom. Symptoms may be episodic. Diagnosis is based on findings in history, laryngoscopy, and, if possible, spirometry during an attack [5; 11]. In a refractory chronic cough population, vocal cord dysfunction is a common finding and may be a manifestation of laryngeal hypersensitivity. Treatment is by speech and language therapy intervention [5].

## REFLUX DISORDER ETIOLOGIES OF CHRONIC COUGH AND THEIR MANAGEMENT

In GERD, retrograde transit of gastric contents into the esophagus leads to troublesome symptoms of heartburn, esophageal chest pain, and regurgitation (i.e., “typical” esophageal symptoms) [133; 134]. Cough is an extraesophageal symptom of reflux disease [11]. Chronic cough has a low, but potential, pathophysiological relationship to reflux disease [133]. Estimated chronic cough due to GERD vary widely (7% to 85%), with higher prevalence in Western than Asian countries [20]. Chronic cough and GERD are both very common conditions and can therefore co-appear without being causally related [99].

GERD was previously considered a leading chronic cough etiology directly caused by the acidity of proximal esophageal refluxate, but patients with chronic cough and healthy controls show similar proximal reflux events [58; 135]. Many patients with chronic cough report GERD symptoms, but PPI therapy is ineffective in those without acidic reflux and only modestly benefit those with typical esophageal symptoms [109].

Reflux can be acidic or non-acidic, liquid or gaseous, and proximal or distal in location. Reflux can trigger cough, coughing can induce reflux, and chronic cough may also cause GERD or increase reflux episodes [20; 134]. PPIs decrease reflux acidity but not reflux events and work poorly in patients with airway or extraesophageal reflux [136]. PPI failure in chronic cough treatment suggests the acidic component of reflux has little effect on chronic cough or its etiology [58].

In extraesophageal reflux, troublesome symptoms not normally considered esophageal manifest in the lower and upper airways as chronic cough, asthma, laryngitis, dysphonia, pulmonary fibrosis, sinus disease, ear disease, postnasal drip, throat clearing, non-cardiac chest pain, or dental erosion [20; 134].

Laryngopharyngeal reflux is defined as the backflow of weakly or non-acidic “mist” or liquid above the upper esophageal sphincter into the upper airways. Due to weaker mucosal defenses in the upper respiratory tract, inflammation of the mucous membranes and epithelial tissue damage occur with exposure to fewer, and less acidic, reflux events. A significant negative effect from pepsin, a gastric enzyme, on oropharyngeal and respiratory tract tissues is also demonstrated [58; 137].

Airway reflux is interchangeably used for laryngopharyngeal, non-acid esophageal, extraesophageal, and silent reflux. But it is important to remember that airway reflux is not GERD. Defined by the symptoms of heartburn and dyspepsia, and associated with esophagitis, GERD is a peptic condition predominantly of liquid acidic reflux [59]. The majority of patients with airway reflux/laryngopharyngeal reflux do not have esophagitis or heartburn [137].

Airway reflux shifts the paradigm from traditional GERD to cough hypersensitivity through sensitization of vagal afferents. Evidence that esophageal irritation by acid and non-acid reflux may directly initiate cough led to the concept of an esophagobronchial reflex based on crosstalk at the nucleus tractus solitarius between esophageal and airway sensory neurons converging in this brainstem area [58].

This led to gastroesophageal reflux-associated cough, a cough-predominant phenotype of GERD, as a chronic airway inflammatory disease. Epithelial damage and airway inflammation in gastroesophageal reflux-associated cough patients suggest micro-aspiration, and the esophagobronchial reflex mediated by distal esophageal vagal afferents [136].

Chronic cough may result from GERD/extraesophageal reflux-induced airway inflammation and supra-esophageal pathology. Whether refluxate causes damage leading to extraesophageal reflux, needs to be acidic or merely contain pepsin, or whether neurogenic signaling leads to inflammation and subsequent symptoms remains unclear [134; 136].

## REFLUX INVESTIGATIONS IN PATIENTS WITH CHRONIC COUGH

Investigation	Description	Utility
24-hour esophageal pH testing	A catheter is inserted nasally into the esophagus with two pH sensors for 24-hour measurement of proximal and distal acid reflux	Does not reliably predict response to PPI therapy
Barium meal	Radiographic test that visualizes the movement of barium liquid. Can detect structural and motility abnormalities of the esophagus, stomach, and duodenum.	May demonstrate a hiatal hernia and document the extent of non-acid reflux not identified on 24-hour pH testing
Manometry	A catheter is inserted to assess motility patterns by measuring the amplitude of contractile events in the esophagus and its sphincters	Impaired peristalsis is more prevalent in patients with chronic cough, consistent with symptoms of esophageal dysmotility
Impedance testing	Intraesophageal probes measure impedance and pH to record acid, weakly acidic, and non-acid reflux events	Non-acid refluxate may be important in chronic cough etiology, but impedance testing is not validated to investigate chronic cough
Upper GI endoscopy	Allows direct inspection of the upper GI tract and biopsy of stomach and duodenum	Often unrevealing; endoscopic evidence of GERD less common with atypical (e.g., chronic cough) vs. typical symptoms
Source: [19]		Table 6

In sum, GERD can directly affect the airways when gastric acid backflows into the esophagus, irritating the proximal esophagus and laryngopharyngeal areas, triggering the cough reflex to clear the airways. Gastric content can indirectly cause chronic cough by stimulating the distal esophagus, resulting in vagus nerve irritation and cough reflex sensitization. Airway reflux may comprise most cases of reflux-induced cough, its extraesophageal symptom hampering diagnosis based on symptoms alone [39].

### Management

#### *What diet and lifestyle modifications are recommended for all patients with known or suspected reflux-related chronic cough?*

As discussed, the role of reflux, esophageal dysmotility, and aspiration in chronic cough is controversial. Studies suggest non-acidic reflux, both liquid and gaseous, may be an etiological factor. However, no tool reliably detects such reflux and diagnosis relies on clinical history supported by validated questionnaires (e.g., the HARQ). Moreover, the high prevalence of esophageal dysmotility in patients with chronic cough suggests esophagopharyngeal reflux rather than GERD may be the problem [10].

Many of the signs and symptoms associated with chronic cough are explicable by reflux and aspiration, including voice change, nasal symptoms, and dysgeusia. Frequent chest infection bronchitis, even frank bronchiectasis, may be the consequence

rather than the cause of cough via repeated aspiration. Unsurprisingly, following aspiration of GI contents there is a neutrophilic or eosinophilic inflammatory response that might be giving rise to asthmatic cough and mucus hypersecretion [10].

The 2016 ACCP clinical practice guideline for reflux-associated chronic cough suggests that esophageal manometry and pH-metry be performed in patients with suspected reflux cough refractory to a three-month antireflux trial and being evaluated for surgical management (antireflux or bariatric); or with strong clinical suspicion warranting diagnostic testing for gastroesophageal reflux (**Table 6**). Esophageal manometry assesses for major motility disorder. It involves placing the pH electrode 5 cm above the lower esophageal sphincter in the pH monitoring study after the patient is off PPIs for seven days and histamine H<sub>2</sub>-receptor antagonists for three days [83].

For overweight and obese patients, treatment of suspected reflux-cough should include diet change to promote weight loss. In all patients, recommended diet and lifestyle modifications include [6]:

- Eliminate coffee, tea, soda, other carbonated beverages, fish oil supplements, chocolate, mints, alcohol, and energy drinks, sports, or other drinks containing citric acid
- Consume no more than 45 grams of fat daily
- Avoid smoking and vaping

- Avoid exercising that markedly increases intra-abdominal pressure
- Elevate the head of the bed and avoid meals within three hours of bedtime

In patients with heartburn and regurgitation, PPIs, histamine H<sub>2</sub>-receptor antagonists, alginate, or antacid therapy is often sufficient to control these symptoms. Gastrointestinal symptoms respond within 4 to 8 weeks, but cough may take 12 weeks to improve [83]. PPI monotherapy is not recommended for chronic cough with solely extraesophageal symptoms, as it is unlikely to resolve the cough.

The ACCP suggests against antireflux surgery for patients with chronic cough patients with a major motility disorder and/or normal acid exposure time in the distal esophagus, as the procedural risks and lack of supporting evidence make the risk-benefit ratio unacceptable [83]. However, surgery may be considered for presumed reflux-cough in patients with normal peristalsis, abnormal esophageal acid exposure on pH-metry, and refractory to medical therapy.

### TREATABLE TRAITS AND THOROUGHNESS

The variable success in managing chronic cough may be due, in part, to guidelines or protocols not being implemented as planned (**Table 7**) [6; 80]. Failure to recognize the complexity of airway diseases can lead to suboptimal outcomes, as diseases with different endotypes can require different therapeutic strategies (precision medicine). Because the treatable traits approach is a label-free approach, it does not start on the assumption that the diagnosis (e.g., asthma, COPD) is well-established and clear, a situation that is not the case in many instances in clinical practice, particularly in primary care. This is a fundamental, but often overlooked, issue in the current guideline-directed management of airway diseases [14; 16].

#### Pulmonary and Extrapulmonary Traits as “Connected Comorbidities”

As discussed, the treatable traits approach encourages trans-diagnostic thinking about chronic cough and associated diseases to identify distinct endotypes and phenotypes within traditional diagnostic categories, as well as shared mechanisms across diagnostic boundaries. For example, asthma and severe chronic rhinosinusitis with nasal polyposis are frequently associated with other, coexisting type 2 inflammatory diseases, such as NSAID-exacerbated respiratory disease, allergic rhinitis, eosinophilic esophagitis, atopic dermatitis, and type 2 eosinophilic COPD [114]. Chronic rhinosinusitis with nasal polyposis has a 7% prevalence in patients with asthma, increasing to 40% in NSAIDs-exacerbated respiratory disease [138]. In predisposed subjects, a dysregulated type-2 inflammation can develop in epithelial barriers (e.g., airways, intestine, skin) in response to various antigens, such as allergens, micro-organisms, and pollutants. This dysregulated epithelial response leads to diseases such as asthma, rhinitis/rhinosinusitis, eosinophilic gastrointestinal disorders, and atopic dermatitis [95].

Allergens are not the only antigens that trigger inflammation. Rather than allergic disorders, type 2 disorders would be a more appropriate definition, also including non-allergic eosinophilic diseases such as nonasthmatic eosinophilic bronchitis, chronic rhinosinusitis, and eosinophilic disorders of the gastrointestinal tract [95].

Targeted biological therapies can also address conditions with shared type 2 pathophysiology. Biologics with FDA approval targeting type 2 inflammatory disease pathophysiology include dupilumab (anti-IL-4 and IL-13), omalizumab (anti-IgE), mepolizumab (anti-IL-5), and benralizumab (anti-IL-5R) [92]. Mepolizumab has proven effective in chronic rhinosinusitis with nasal polyposis and asthma with high eosinophil levels in sputum. Dual targeting of IL-4 and IL-13 by dupilumab has shown efficacy across chronic rhinosinusitis with nasal polyposis, asthma, eosinophilic esophagitis, and atopic dermatitis, and in uncontrolled COPD with high eosinophil counts [93]. Chronic cough, it should be stressed, has not been examined in any study of biological therapies.

#### The Argument for Thoroughness

The optimal clinical approach in chronic cough and refractory chronic cough continues to evolve. The ERS guideline suggests simplifying the diagnostic process to shorten a patient’s journey to a diagnosis of refractory/unexplained chronic cough and limiting sequential empiric trials to two to four weeks unless responses are observed [10]. However, the 2023 BTS guideline and others argue for a more assertive approach to identify all treatable traits and maximize therapy response before diagnosing refractory/unexplained chronic cough [5; 78]. This would be the counterargument to the diagnostic-therapeutic empiric trials approach.

In a 2024 study, all 201 patients presenting to a cough center in 2018–2022 were prospectively studied. Refractory chronic cough (defined as persistent cough severity VAS  $\geq 40$  with little improvement after at least two treatment attempts) was diagnosed in 30.7% and unexplained chronic cough in 1.5% [78]. The authors suggest a thorough diagnostic algorithm, with frequent second-step investigations, enabled diagnoses of less common cough etiologies and the low (1.5%) unexplained chronic cough rate. As many therapeutic trials as necessary were engaged in order to target all identifiable treatable traits of chronic cough. Treatment followed a stepwise intensification of therapy and introduced add-on treatment of all cough causes, but this was time-consuming and related to difficulties in keeping patients’ adherence. In routine practice, the authors usually recommend more than two therapeutic trials before diagnosing refractory chronic cough. When refractory/unexplained chronic cough is diagnosed, additional treatments should be initiated. These patients require nonpharmacologic and/or drug therapies with opioids, neuromodulators, or novel refractory chronic cough agents.

## PITFALLS IN THE MANAGEMENT OF CHRONIC COUGH

### Upper Airway Cough Syndrome

Failing to recognize that upper airway cough syndrome (also asthma or GERD) can present as a cough-phlegm syndrome, misdiagnosed as chronic bronchitis.

Assuming that all histamine H1 receptor antagonists (H1RAs) are the same. H1RAs without anticholinergic activity do not help nonallergic rhinitis conditions. Further, anticholinergic H1RAs may adversely affect memory, glaucoma, and prostate problems. Instead, consider ipratropium bromide nasal therapy.

Failing to consider:

- “Silent” upper airway cough syndrome when a patient does not sense a postnasal drip or realize their frequent throat clearing
- Allergic rhinitis and recommend the avoidance of allergens because symptoms are perennial
- Sinusitis because it is nonobvious
- NSAID-exacerbated disease
- The potentially beneficial role of upper respiratory endoscopy

### Asthma

Failing to recognize that:

- Asthma can present as cough alone (i.e., cough-variant asthma)
- Inhaled medications may exacerbate cough
- Positive methacholine challenge alone is not diagnostic of asthma

### Nonasthmatic Eosinophilic Bronchitis

Failing to consider the diagnosis, occupational/environmental causes, or order the correct test

### GERD

Failing to recognize that:

- “Silent” reflux disease can be causal and that it may take two to three months of intensive treatment before cough starts to improve and five to six months to resolve
- GERD can be worsened by comorbidities (e.g., obstructive sleep apnea) or their treatment (e.g., nitrates or calcium channel blockers for coronary artery disease, progesterone for hormone replacement)

Assuming that:

- Cough cannot be due to GERD because cough remains unchanged when gastrointestinal symptoms improve
  - Vocal cords’ appearance can diagnose GERD, when inflammatory changes from coughing can mimic those of reflux
- Being unaware that acid suppression alone will not improve cough

Failing to consider:

- Non-acid reflux disease
- The role of diet, intense exercise, and prokinetic therapy
- Adequately treat co-existing causes of cough that perpetuate the cycle of cough and reflux because cough can provoke reflux

### Triad of Upper Airway Cough Syndrome, Asthma, and GERD

Failing to consider that more than one condition may be contributing simultaneously to cough, or failing to consider additional contributing conditions because of another “obvious” cause (e.g., COPD)

Failing to appreciate:

- These chronic disorders cannot be cured and will periodically flare, especially with viral illness
- When cough flares after a period of remission, re-evaluate as if a new problem
- Asthma may become a problem when it was not before

### Unsuspected Airway Diseases

Failing to perform bronchoscopy when chest x-ray and CT are normal. Transnasal route allows inspection of both upper and lower respiratory tracts.

Failing to appreciate that prolonged IV therapy for suppurative airway disease may succeed when the same drug given orally failed

Source: [6; 80]

Table 7

In a separate study conducted at a clinic in China, experts found that among 1,554 patients with chronic cough patients with negative chest x-rays, 58.8% were attributable to common causes, including nonasthmatic eosinophilic bronchitis (18.3%), cough-variant asthma (16.3%), gastroesophageal reflux-associated cough (13.2%), and upper airway cough syndrome (11.1%) [139]. In addition, 18.4% of cases were attributable to other causes: chronic bronchitis (6.1%), bronchiectasis (4.5%), atopic (4.4%), and postinfectious (3.5%) cough; 9.6% had chronic cough of unexplained etiology. Finally, 13.1% of cases were due to rare causes (e.g., bacterial bronchitis, somatic cough syndrome, diffuse panbronchiolitis, obstructive sleep apnea, and interstitial lung disease). These findings suggest that special examinations should be considered after excluding common causes of chronic cough.

It is important to remember that the workup to rule out refractory/unexplained chronic cough is not complete until bronchoscopy has been performed [6]. A study of bronchoscopy involving 54 patients with refractory/unexplained chronic cough with sputum production (more than 1 tbsp/day), atypical urge-to-cough sensations in chest, and unremarkable chest CT revealed bronchoalveolar neutrophilia in 84% and excessive dynamic airway collapse in 31% [140]. Bronchoscopy influenced or changed the management in 89% of patients. Bronchoscopy findings in this specific population have rarely been described, and treatment strategies in these patients differ from typical refractory/unexplained chronic cough. Bronchoscopy provides high diagnostic value in refractory/unexplained chronic cough with mucus production, identifying specific treatable traits of neutrophilic airway inflammation and excessive dynamic airway collapse [140].

Another argument for moving away from the routine use of empiric therapeutic-diagnostic trials is to spare patients with chronic cough from exposure to minimally helpful or unhelpful medications with potentially adverse effects. For example, PPIs are recommended against for chronic cough in patients who lack classic GERD symptoms. Cumulative doses of PPIs dose-dependently increase the risk of developing hypomagnesemia and other side effects. Both hypomagnesemia and its consequent decrease in melatonin production can decrease lower esophageal sphincter tone and trigger a paradoxical iatrogenic cough. Rather than PPI dose escalation for partial responders, magnesium and melatonin supplementation is recommended to curtail side effects of long-term PPIs [104].

Oral corticosteroids, due to their substantial cumulative side effects, are now recommended only as a last resort in the most recent asthma treatment guidelines [141; 142]. Even occasional short courses of oral corticosteroids are associated with significant short-term and cumulative long-term adverse effects, with a pronounced dose-response. Short-term adverse effects of oral corticosteroids include sleep disturbance, increased appetite, reflux, mood changes, sepsis, pneumonia, and thromboembolism. As few as four to five lifetime courses of oral corticosteroids are associated with a significantly increased dose-dependent risk of diabetes, cataracts, heart failure, osteoporosis, and several other conditions [142].

## TREATMENT OF REFRACTORY CHRONIC COUGH

*What pharmacotherapeutic agents are recommended for the treatment of refractory or unexplained chronic cough?*

Refractory and unexplained chronic cough are diagnoses of exclusion. For cases with no clear etiology after an extensive workup, or when guideline-based treatment improves the presumed underlying cause of coughing but not the chronic cough itself, cough hypersensitivity syndrome is the most likely explanation [39].

A variety of organizations have published guideline recommendations for the treatment of refractory and/or unexplained chronic cough (**Table 8**). The British Thoracic Society asserts that cough hypersensitivity is a treatable trait of many conditions and often the foremost problem in patients with chronic dry/unproductive cough [5]. However, there are currently no tools to positively identify cough hypersensitivity. If the condition does not improve with treatment of treatable traits, it is considered refractory chronic cough. In these patients, the most effective treatments are those addressing cough hypersensitivity and include low-dose morphine, gabapentin, and nonpharmacological therapy. In addition, novel therapies are in development, with P2X3 antagonists the most promising [5].

### PHARMACOTHERAPY

Neuromodulators are centrally acting agents for refractory chronic cough that can downregulate the hypersensitive cough reflex to decrease coughing. Neuromodulators are first-line options for refractory chronic cough [39; 57]. However, some of the literature on neuromodulator use in patients with refractory chronic cough might seem counterintuitive.

Clinical trials of P2X3 antagonists have shown efficacy in reducing cough frequency in many patients with refractory/unexplained chronic cough, but the exact mechanisms underlying refractory/unexplained chronic cough remain poorly understood. Although data also suggest central mechanisms may be a key component in the pathophysiology of refractory/unexplained chronic cough, antitussive drug development has focused on peripheral targets [143].

Among patients with unexplained chronic cough started on amitriptyline and contacted by mail two to three years later, 64% had stopped the medication due to no improvement (40%) and/or side effects (48%). The most common side effects triggering treatment nonadherence were sedation (18%), dry mouth (18%), anxiety (8%), difficulty sleeping (8%), and dizziness (5%). Combining patients who continued and stopped amitriptyline, 53% reported cough improvement of at least 50%. There is some evidence that as treatment duration increases, amitriptyline efficacy may decrease [144].

GUIDELINE RECOMMENDATIONS FOR NEUROMODULATOR TREATMENT OF REFRACTORY/UNEXPLAINED CHRONIC COUGH						
Drug	Guideline Organization (Year)					
	ACCP (2016)	ERS (2020)	GRS (2020) <sup>a</sup>	FRS (2023)	BTS (2023)	NEURO-COUGH (2023)
Low-dose morphine slow-release	Not reported <sup>b</sup>	Strong recommendation	Strong recommendation	Recommended: Grade B	Recommended	Recommended, very high consensus
Codeine	Not reported	Not recommended	Not reported	Not reported	Recommended against	Not reported
Gabapentin	Recommended	Conditional recommendation	Can be used	Recommended: Grade B	Recommended	Recommended, high consensus
Pregabalin	Not reported	Conditional recommendation	Can be used	Recommended: Grade B	Recommended	Not reported
Amitriptyline	Not reported	Not reported	Can be used	Recommended: Grade C	Not reported	Recommended, high consensus
Baclofen	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

<sup>a</sup>“Can be used” is a weaker endorsement than “recommendation” (i.e., “should be used”).  
<sup>b</sup>75% of expert panelists endorsed a recommendation of morphine, falling short of 80% required for inclusion; thus, morphine is neither recommended for nor against.  
ACCP = American College of Chest Physicians; BTS = British Thoracic Society; ERS = European Respiratory Society; FRS = French-Speaking Society of Respiratory Diseases; GRS = German Respiratory Society; NEURO-COUGH = New Understanding in the treatment Of COUGH Clinical Research Collaboration; SR = sustained-release.

Source: [5; 10; 11; 12; 18; 86] Table 8

## Opioid Medications

The concept of chronic cough as a neuropathic condition, treated with neuromodulators, is not new. In 1856, Edward Smith described chronic cough as a “disease in itself” due to “irritability of the nerves” that could be treated with “morphia,” 164 years before expert consensus in the European Respiratory Society chronic cough guidelines concluded the same, albeit for refractory chronic cough [10; 111]. Opioids are thought to exert antitussive effects through opioid receptors within inhibitory cortical descending pathways [59].

### Codeine

Codeine is a weak opioid that is metabolized to morphine (5% to 10%) by the enzyme cytochrome P450 2D6 (CYP2D6) in the liver to produce its antitussive effects [145]. Codeine has long been used as an antitussive, but a minority of the population possess a genetic variation in CYP2D6 activity, with variable and unpredictable metabolism that increases unpleasant side effects and decreases efficacy. Codeine is now considered an unreliable antitussive and should not be used in chronic cough [5].

### Low-Dose Morphine Slow-Release (SR)

Morphine is not affected by interindividual variability in CYP2D6 metabolism; thus, its biological effects are more predictable than codeine [146]. In the first positive results from a double-blind randomized controlled trial for any drug therapy of refractory chronic cough, morphine was selected to minimize the variability of codeine [25; 147]. This study compared twice-daily slow-release morphine 5 mg with placebo for four weeks, followed by four weeks of crossover to the alternate treatment. A three-month open-labeled extension of the randomized controlled trial allowed dose escalation to 10 mg twice per day if patients thought their cough was inadequately controlled [147].

The mean LCQ score significantly improved on morphine but not placebo, with significant improvement in physical, psychological, and social subdomains. A 40% reduction in daily cough scores was noted with morphine; placebo had no discernable effect over baseline. Of patients entering the extension, 67% opted for dose escalation and, after three months, had cough outcome improvements similar to 5-mg full-responder patients.

Side-effects of constipation (40%) and drowsiness (25%) were tolerable; no patient dropped out from adverse events. Sedation, previously believed to explain the antitussive action of morphine, was transient, but the antitussive effect continued throughout the core and extension study phases [147].

The authors of this study state that side effects and dependence are obvious concerns with opioid therapy for what is a disabling but non-life-threatening condition. However, they note that the risk-benefit ratio makes low-dose slow-release morphine a credible therapeutic option in patients with refractory chronic cough for whom other treatments have failed. Comparisons of similar therapeutic options were made with patients who require long-term oral corticosteroids for severe nonasthmatic eosinophilic bronchitis or cough-variant asthma with a consequently worse adverse event profile [147].

Another double-blind crossover study randomized previous morphine responders to slow-release morphine 5–10 mg twice daily or placebo. After five days, morphine reduced 24-hour cough frequency by 72% over placebo, including overnight (83%) and daytime (71%) cough frequency [148]. Morphine also significantly reduced noxious somatic sensations driving the urge to cough, suggesting this may be an important component of opioid modality in refractory chronic cough [149].

In a real-world effectiveness and tolerability study of long-term, low-dose opioids, 100 patients were prescribed twice daily slow-release morphine 5–10 mg (72%), oxycodone, or oxycodone/naloxone for a median 52 weeks for refractory/unexplained chronic cough. Median cough severity score (CSS, on a 0–10 scale) decreased from 8 pre-treatment to 4. In all, 60% had good-to-excellent response, while 25% had no response. Side effects (present in 38%) were most commonly constipation (25%), which was managed with dose reduction or constipation therapy; however, 15% stopped treatment due to side effect intolerance. Low-dose opioids improved long-term cough outcomes and were tolerated by most patients with refractory/unexplained chronic cough, but managing constipation allowed more patients to continue therapy [150].

Clinical experience with low-dose, slow-release morphine suggests that up to 50% to 60% of patients with refractory chronic cough obtain benefit [5; 59; 150]. Response dichotomizes into either a large effect on cough symptoms or no effect at all and is usually apparent within five days. The main side effect, constipation, can be managed with laxatives or adding oral low-dose naloxone. Once-daily dosing may be sufficient if cough symptoms are mainly troublesome during waking hours or overnight. Antitussive tolerance does not seem to develop. Unlike in severe chronic pain, there appears to be a dose ceiling for slow-release morphine of twice daily 10 mg, with no further antitussive effect beyond this. Concerns remain about misuse/addiction potential, and patients must be carefully monitored [5; 59]. As noted in a 2024 review, it is unclear why such low doses, compared with those used for analgesia, are effective in some patients with refractory chronic cough [25].

## Gabapentinoids

Gabapentin and pregabalin are synthetic analogs of gamma-aminobutyric acid (GABA) that bind the  $\alpha 2\delta$  subunit of voltage-gated calcium channels to block excitatory neurotransmitter release. Both were developed originally for epilepsy treatment and subsequently found to ameliorate chronic neuropathic pain, which is associated with central sensitization. The similar pathophysiologic mechanisms of chronic neuropathic pain and chronic cough suggested that gabapentin and pregabalin may also be beneficial in patients with refractory chronic cough [151].

Gabapentin (1,800 mg/day or the maximum tolerable dose) was compared with placebo for eight weeks in a double-blind randomized controlled trial of 62 patients with refractory chronic cough. Gabapentin significantly improved LCQ score over placebo by 1.8 points, and significantly reduced objective cough frequency and cough severity over placebo. Gabapentin response was greater in patients with symptoms of central sensitization (e.g., laryngeal paresthesia, allotussia, hypertussia). The onset of action of gabapentin took up to four weeks [152]. It was subsequently noted that cough frequency differed between gabapentin and placebo groups at baseline (45.3 vs. 68.8 coughs per hour) and was measured only for one hour at each assessment visit, making interpretation of cough frequency outcomes difficult [25; 146].



EVIDENCE-BASED  
PRACTICE  
RECOMMENDATION

The European Respiratory Society suggests a trial of gabapentin or pregabalin in adults with chronic refractory cough.

(<https://erj.ersjournals.com/content/55/1/1901136>. Last accessed August 12, 2024.)

**Strength of Recommendation/Level of Evidence:**  
Conditional recommendation, low-quality evidence

An open-label randomized trial compared gabapentin (300 mg three times per day) to baclofen (20 mg three times per day), an antispasticity drug, in 234 patients with refractory gastroesophageal reflux-associated cough over nine weeks. Compared with baseline, gabapentin and baclofen similarly led to decreased cough symptom scores and patients with success for cough resolution (57.3% vs. 53.0%). Gabapentin led to lower side effect rates than baclofen of somnolence (20% vs. 35%) and dizziness (11% vs. 24%) [151]. In addition to other burdensome side effects, sudden discontinuation of baclofen can result in seizures [5].

In another study, twice daily pregabalin 75 mg was prescribed to 50 consecutive patients with refractory or unexplained chronic cough for three months. Pregabalin response, defined as LCQ total score improvement of  $\geq 1.3$ , was attained by 56% of patients. Responders were more likely to have refractory



(with underlying pulmonary disease) than unexplained chronic cough, and on average were more symptomatic at baseline. There was no information on side effects or dropout [153].

In another study, 40 patients with refractory chronic cough were randomized to speech pathology treatment plus pregabalin 300 mg/day or speech pathology treatment plus placebo for four weeks. Compared with the placebo group, those who received speech pathology treatment/pregabalin experienced a statistically significant improvement [154]. However, CNS adverse effects (e.g., dizziness, disorientation, confusion, fatigue, blurred vision) were common and sometimes intolerable. The effects of pregabalin on 24-hour cough frequency outcome were non-significant [146].

Because gabapentinoids have beneficial effects on anxiety, improvements in mood may contribute to the apparent benefit or changes in symptom perception or cough intensity. Side effects are common, wide ranging, and can be difficult for patients to tolerate. Slow dose escalation may help minimize this, and maximal doses may not be needed to afford some improvement in cough. Gabapentin and pregabalin may have abuse potential in susceptible patients [5].

Gabapentin should be started at a low dose (e.g., 100 mg three times per day) and titrated up to a maximum dose (600 mg three times per day), depending on clinical effects and tolerability. The usual starting dose of pregabalin for chronic cough is 25 mg twice daily, with increases in increments to a maximum 75 mg twice daily. Patients should be reassessed during dose titration and therapy stopped if there are significant side effects or inadequate response to treatment [5].

In clinical experience, the minority of patients who achieve cough suppression often do so at the expense of intolerable adverse effects, usually sedation [57]. Among 38 patients prescribed gabapentin (maximum: 1,800 mg per day) or pregabalin (maximum: 300 mg per day) for refractory chronic cough, 24% developed immediate intolerable side effects and 37% tolerated the drugs but had no response and stopped the medication. Among the 39% with an initial favorable response, 18% eventually developed intolerable side effects and 21% were able to continue with therapy long-term. The most common side effect was drowsiness/sedation. In real-world practice, gabapentinoids are effective in a subgroup of patients with refractory chronic cough, but side effects may outweigh their potential benefits, which were intolerable for 42% of patients [155].

### Tricyclic Antidepressants

Amitriptyline and nortriptyline are tricyclic antidepressants with a broad range of pharmacologic actions effecting adrenergic, serotonergic, muscarinic, and histaminergic systems. Amitriptyline is also used in chronic neuropathic pain (e.g., migraine, postherpetic neuralgia, painful diabetic neuropathy) and has been suggested to be effective in the treatment of chronic cough, with anticholinergic properties thought

to underlie the antitussive effect [57; 156]. However, clinical experience with amitriptyline in refractory chronic cough suggests more limited value [5].

In a small randomized trial of patients attending an otolaryngology clinic with postviral refractory chronic cough, amitriptyline 10 mg per day was compared with codeine 10 mg/guaifenesin 100 mg combined in a syrup taken every six hours. The majority of patients reported a 75% to 100% improvement in cough with amitriptyline, while most reported no improvement with codeine/guaifenesin. Compared with the control arm, amitriptyline was significantly associated with a response greater than 50% [157]. In a randomized controlled trial of patients with chronic pharyngolaryngeal neuropathy, 67% had subjective improvement with amitriptyline (up to 50 mg/day), compared with 44% with placebo. The mean Voice Handicap Index-10 (VHI-10) score worsened with amitriptyline but was unchanged with placebo. Attrition over the eight-week trial was 40% [158].

Nortriptyline was studied in 42 patients with neurogenic chronic cough, of whom 45% discontinued nortriptyline due to side effect intolerance or lack of response. The average time to clinical response was 5.5 months. The average minimum effective dose was 21 mg per day in responders. Laryngeal asymmetry was present in 85.7% of all patients. Side effects included sedation, xerostomia, and anxiety. The intolerability was surprising, because nortriptyline is both a metabolite of amitriptyline and reported to be better tolerated [159].

### Pharmacotherapy for Chronic Cough in Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis is a chronic, progressive, and invariably fatal fibrotic lung disease, and 85% of patients with idiopathic pulmonary fibrosis experience cough, a distressing symptom associated with rapid disease progression. Available treatments for idiopathic pulmonary fibrosis slow disease progression but do not improve symptoms or quality of life. Thalidomide benefitted idiopathic pulmonary fibrosis cough in one randomized controlled trial, but its side effect profile renders it practically useless, as only 20% of patients were able to tolerate it [125]. Worse still, the potentially severe adverse effect of peripheral neuropathy suggests it may damage sensory nerves (vagal afferents). Thalidomide should not be considered even as second-line therapy for idiopathic pulmonary fibrosis cough until further evaluation of the benefit/risk ratio has been undertaken [160].

Although studies on refractory chronic cough can help inform the treatment of idiopathic pulmonary fibrosis cough, the biological mechanisms that contribute to cough probably differ in these conditions, as evidenced by the contrasting results with gefapixant, a P2X3 receptor antagonist, in refractory chronic cough (positive findings) and idiopathic pulmonary fibrosis cough (negative findings) [161].

### Nalbuphine

Nalbuphine extended-release (ER) is an opioid agonist-antagonist. In a double-blind randomized controlled trial of patients with idiopathic pulmonary fibrosis and chronic cough, nalbuphine ER tablets (titrated up to 162 mg twice daily) led to 75.1% reduction in daytime objective cough frequency, compared with 22.6% with placebo, a 50.8% placebo-adjusted reduction in 24-hour cough frequency, and similar improvements in patient reported outcomes [162]. Nalbuphine ER was the first therapy to show robust effects on chronic cough in idiopathic pulmonary fibrosis [25]. However, nalbuphine side effects of nausea (42.1%), fatigue (31.6%), constipation (28.9%), and dizziness (26.3%) led to a 24% dropout during the drug initiation phase, partially attributed to the inflexible forced-titration study design [162].

### Low-Dose Morphine SR

In a multicenter randomized controlled trial of patients with idiopathic pulmonary fibrosis and chronic cough, low-dose, slow-release morphine (5 mg twice daily) reduced objective awake cough frequency by 39.4% over placebo, and all cough-related patient-reported outcomes remained significantly improved when adjusted for placebo. Morphine side effects of nausea (14%) and constipation (21%) resulted in only one participant discontinuing morphine, indicating tolerability for these patients. The authors note that the safety assessments during study visits were reassuring and there appeared to be no changes in mood or excessive fatigue with morphine [161]. The authors advocate for rapid implementation in clinical practice due to the well-established safety profile and worldwide availability [163].

A 2024 study reported variable effectiveness of slow-release morphine (8–32 mg per day) in reducing breathlessness in patients with COPD. But, it provided reassuring safety data by observing no evidence of harm and no worsening of subjective daytime sleepiness, alertness, or sleep quality at one and four weeks in these severely ill patients [164].

## INVESTIGATIONAL PHARMACOTHERAPIES

Low-dose, slow-release morphine has the strongest observational and empirical evidence of antitussive benefit in refractory chronic cough of any commercially available (although off-label) medication and may be used safely in this population when patients are carefully screened and monitored. Because as many as 50% of patients with refractory chronic cough have no response to low-dose morphine and with substantial restrictions on opioid prescribing in the United States, effective peripherally acting antitussives are an urgent priority for investigators.

### P2X3 Receptor Antagonists

P2X3 receptors form ion channels containing ATP-binding sites. In the lungs and airway, ATP activates P2X3 receptors localized on vagal sensory nerve terminals, resulting in bronchoconstriction, cough, and localized release of inflammatory neuropeptides [165].

A breakthrough occurred when gefapixant, a P2X3 receptor antagonist, demonstrated a dramatic reduction in chronic cough. Other P2X3 antagonists confirmed the efficacy of this drug class in refractory chronic cough. The endogenous ligand for P2X3 is ATP. Epithelial damage is believed to release ATP. Evidence suggests that ATP largely mediates peripheral hypersensitivity; therefore, gefapixant is peripherally acting in refractory chronic cough [166].

P2X3 receptors are ion channels found on sensory afferent nerve fibers, activated by ATP. In preclinical studies, vagal C fibers, including those thought to be important in mediating cough, have been shown to express P2X3 and P2X2. At present, it is unclear whether ATP concentrations are elevated or P2X3 receptor expression increased in the airways of patients with refractory chronic cough, or how antagonism of P2X3 plays a role in reducing coughing to a range of chemical irritants, temperature changes, and mechanical stimuli. Nonetheless, in clinical trials, P2X3 receptor antagonism has provided robust reductions in cough frequency and patient-reported outcomes [25].

### Gefapixant

The first novel therapy to have significant effects in patients with refractory chronic cough was gefapixant, a first-in-class P2X3 antagonist that was originally planned to be developed as an analgesic. Gefapixant has become the first therapeutic to undergo systematic development as a treatment for refractory chronic cough following unprecedented reductions in cough frequency.

In a landmark study, twice daily gefapixant 600 mg showed remarkable therapeutic effects in patients with refractory chronic cough [167]. Objective 24-hour cough frequency was reduced 74% compared with placebo, and daytime cough severity VAS score and CQLQ score reduced by -25.6 and -9.2, respectively. However, another important finding was that virtually all treated patients reported ageusia, or loss of taste, and 24% withdrew because of the adverse effect. These taste side effects are likely attributable to the inhibition of P2X2/3 channels on the nerve fibers innervating the taste buds by high-dose gefapixant [146].

Subsequent studies suggest that antitussive effects are retained at much lower doses (30–50 mg twice daily), at which taste was altered rather than lost and hence the therapy was better tolerated. Larger multi-center parallel group studies were performed in the UK and the United States followed by the first-ever global phase 3 trials of an antitussive treatment for refractory chronic cough, which reported positive findings over placebo for a 45-mg twice daily dose [25].

### **Eliapixant and Filapixant**

Following the taste side effects reported for gefapixant, more selective P2X3 antagonists were evaluated for the treatment of refractory chronic cough; however, there was some uncertainty about whether effects at both P2X3 and P2X2/3 channels were both contributing to antitussive efficacy and hence whether more selective agents would have similar efficacy. Eliapixant and filapixant both demonstrated efficacy in dose-ranging studies, but eliapixant appeared to cause less taste disturbance (up to 21% of patients) and was therefore progressed to a phase 2b parallel trial. Although this trial reported positive findings, a small number of cases of liver toxicity prevented further development of this therapy for refractory chronic cough [25].

### **Sivopixant**

Another more selective P2X3 antagonist, sivopixant, exhibited promising findings in a single-dose crossover study, very similar in design to the first gefapixant study. The reduction in daytime cough frequency of 32% over placebo (the primary endpoint) was not quite statistically significant, but taste adverse effects were only reported in 6.4% of patients. In a follow-up, multi-center parallel group study assessing a range of doses for four weeks, no dose of sivopixant could be discriminated from the very large placebo effect—there was 60% placebo reduction in cough frequency from baseline. The largest absolute change in cough frequency was observed for the highest dose (300 mg), but 30% of patients reported taste adverse effects. No further studies of sivopixant in refractory chronic cough have been planned [25].

### **Camlipixant**

Finally, thought to be the most selective P2X3 antagonist, camlipixant is the second compound in this class to be evaluated in phase 3 trials. The first double-blind randomized controlled crossover trial of camlipixant studied escalating doses from 25 mg to 200 mg versus matched placebo. Although the primary endpoint of awake cough frequency did not reach statistical significance, preplanned subgroup analysis in patients with a cough frequency of at least 20 coughs per hour (80% of patients) and those with greater than the median cough frequency ( $\geq 32$  coughs per hour, 50% of patients) exhibited significant improvements versus placebo for all doses tested. This preplanned analysis was based on observations from several of the gefapixant studies that suggested P2X3 antagonism was most efficacious in patients with the highest baseline cough frequency [25].

In post-hoc analysis of a phase 2a study, among patients who reported cough-related urinary incontinence at baseline, 11%, 15%, and 21% of those treated with 12.5 mg, 50 mg, and 200 mg camlipixant, respectively, reported no cough-related urinary incontinence at day 29 (compared with 3% with placebo) [168]. As of 2024, camlipixant is being evaluated in two large-scale phase 3 studies, again in patients selected for higher cough frequencies [25].

### **Other Novel Antitussives Under Investigation**

The studies completed to date investigating P2X3 antagonists have typically found that between one-quarter and one-third of patients do not experience the 30% reduction in cough frequency thought to be the meaningful clinical threshold, suggesting some heterogeneity in the mechanisms underlying refractory chronic cough. Furthermore, patients with less frequent/severe coughing than those recruited to these trials may not benefit from treatments interrupting the ATP-P2X3 axis. Therefore, treatments with alternative modes of action are required to optimally manage patients with refractory chronic cough [25].

### **Sodium Channel Blockade**

Lidocaine non-selectively blocks voltage-gated sodium channels important in the initiation of action potentials and their conduction and is a local anesthetic agent in routine topical use to reduce coughing during bronchoscopy. Case reports and case series have also described the use of nebulized lidocaine as an antitussive to treat refractory chronic cough [169].

In a three-way crossover study of single-dose lidocaine in refractory chronic cough, lidocaine throat spray reduced coughing by about 50% and was more effective than nebulized lidocaine, probably because nebulization into the lower airways has an irritant effect and evokes coughing initially [169]. The antitussive effects of lidocaine spray are relatively short lived and also associated with numbness in the mouth and lips, preventing patients from safely eating after treatment. Efforts have been made to develop similar therapies with a longer duration of action and without loss of sensation [25].

A novel approach to sodium channel blockade has been developed using a compound that is only active in blocking sodium channels after entering neurons via large-pore ion channels, such as P2X3 channels. As of 2024, a phase 2a clinical trial has been performed but the results are not yet published.

### **TRPM8 Agonism**

Activation of TRPM8 ion channels produces cooling sensations. One new therapy has used an orally dissolving tablet containing a TRPM8 agonist (AX-8) placed on the back of the tongue to act as a counter irritant to the sensations of throat irritation reported by many patients with refractory chronic cough. In a randomized controlled trial, AX-8 reduced cough frequency, but not significantly over eight hours, the duration of action suggested by a previous open-label study. However, the effect was significant over four hours and exaggerated in those patients reporting greater throat discomfort, consistent with the proposed mechanism of action. Further studies in this subgroup of patients are hoped to confirm efficacy [25].

On day 1, AX-8 reduced cough frequency within 15 minutes and more than placebo over two and four hours, but not eight hours. In participants with baseline throat discomfort, reduction in cough frequency was significant over 24 hours, with a maximum reduction compared to placebo of 43% over two hours. Over 14 days, AX-8 significantly improved patient-reported outcomes and the safety profile was good with no serious adverse events. This suggests that TRPM8 agonism has potential for control of refractory/unexplained chronic cough as an alternative or adjunct to other therapies, especially in those patients complaining of cough driven by throat sensations [170].

### **NK-1 Antagonism**


Following a positive study testing aprepitant as a cough treatment in patients with lung cancer, there has been interest in the potential antitussive effects of centrally acting neurokinin-1 (NK-1) antagonists. Following a negative trial in refractory chronic cough, a double-blind randomized controlled trial is in progress testing the effects of orvepitant in patients with cough associated with idiopathic pulmonary fibrosis [25].

## **NONPHARMACOLOGIC THERAPY**

### **Speech and Language Therapy**

Speech and language therapy techniques were first described as improving chronic cough in a randomized controlled trial in 87 patients with refractory chronic cough. The intervention appeared to have positive impact on cough, voice, throat symptoms, and symptom limitation after four therapy sessions over two months. Another study investigated a similar intervention delivered by speech and language therapists and physiotherapists. Compared with sham therapy, LCQ score improved by 1.5 points. Cough frequency improved by 40% more than in the sham-treated arm at four weeks and seemed to be maintained at three months. No larger-scale trials have been completed [25].

Speech and language therapy is a complex intervention, comprising components of education, cough suppression techniques, vocal hygiene, and psychoeducational counseling. Thus, it is difficult to standardize the intervention, and it is not clear whether all or just some of the components are essential for efficacy. In practice, the therapy seems to be most effective when delivered by experienced therapists, who may not be widely available. There is also a question about the durability of the effects over longer timescales when patients may not continue to practice the techniques [25].



The European Respiratory Society suggests a trial of cough control therapy (physiotherapy/speech and language therapy) in adult patients with chronic cough. (<https://erj.ersjournals.com/content/55/1/1901136>. Last accessed August 12, 2024.)

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

The speech and language therapy approach to the management of chronic cough involves four steps: education, vocal hygiene, cough control/suppression training, and psychoeducational counseling [19].

### **Education**

Patients are provided education on the biology of coughing, chronic cough, and cough hypersensitivity. The negative effects of repeated coughing and throat clearing are explained [19].

### **Vocal Hygiene**

Vocal and laryngeal hygiene and hydration are advised with a reduction in caffeine and alcohol intake. Nasal breathing with nasal douching may be recommended with nasal steam inhalation [19].

### **Cough Control/Suppression Training**

Following identification of patient cough triggers, patients are taught a range of suppression strategies, including forced/dry swallow, sipping water, chewing gum, or sucking non-medicated sweets. Breathing pattern re-education is used to promote relaxed abdominal breathing while inhaling through the nose [19].

### **Psychoeducational Counseling**

Behavior modification is used to reduce over-awareness of the need to cough and facilitate an individual's internalization of control over their cough and to help manage stress and anxiety [19].

### Local Injection Therapies

The experience of superior laryngeal nerve block by the injection of local anesthetic agents and corticosteroids has been described retrospectively following implementation in several clinics. In 2024, a small single-blind placebo-controlled study was performed comparing this treatment in 10 patients injected with active treatment and 7 with placebo, finding improvements in cough VAS and LCQ scores. Transient sensations of globus (lump in the throat) and soreness at the site of inject were the main adverse effects. Laryngeal botulinum toxin injections have also been reported to produce improvements in series of patients in clinical care, but no controlled studies have been performed. The broad safety of these interventions and duration of any effect currently remains unclear [25].

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### CONCLUSION

Chronic cough affects roughly 10% of adults in the United States [32]. These individuals can cough hundreds to thousands of times every day, often with uncontrollable bouts of coughing triggered by laughing, speaking, or changes in ambient temperature. This can continue for many years or decades, leading to substantial physical and emotional symptoms, including fatigue, urinary incontinence, cough syncope, dysphonia, depression, anxiety, embarrassment, social isolation, and severely diminished quality of life [28; 40; 64].

In 20% to 59% of patients with chronic cough, coughing persists despite extensive guideline-recommended evaluation and treatment of comorbidities or an underlying cause of cough cannot be identified. In these cases, a diagnosis of refractory or unexplained chronic cough is rendered [7; 36].

Chronic cough is a distinct pathologic entity (cough hypersensitivity syndrome) that develops when repetitive activation of airway cough receptors (typically by inflammatory mediators) induces neuroplastic changes, resulting in peripheral and central sensitization with symptoms of allotussia, hypertussia, and/or laryngeal paresthesia [3; 19; 20]. Hypersensitivity of vagal afferent neurons in the airways and their central projections, and deterioration in cortical inhibitory control of cough, explain the chronicity characteristics of this condition [33; 78].

According to current best evidence, clinical management of patients with chronic cough requires that clinicians perform thorough history, physical examination, and diagnostic testing to identify any potential underlying causes, with asthma, COPD, nonasthmatic eosinophilic bronchitis, upper airway cough syndrome, and GERD the top diagnoses to consider. After assessment is complete, clinicians should treat any identified airway and esophageal conditions according to practice guidelines. As part of the treatment approach, behavioral treatable traits, including cigarette smoking, use of ACE inhibitors and NSAIDs, poor inhaler technique (when relevant), and treatment adherence in general should be identified and addressed [5; 6; 10; 18; 24; 25; 79; 171].

It is important to recognize that cough hypersensitivity syndrome is present when cough persists despite etiologically based treatment or no etiology can be identified. Clinicians can make a diagnosis of refractory or unexplained chronic cough and refocus management to downregulating a hyper-reactive cough reflex using commercially available medication prescribed off-label and cough-specific speech and language therapy [5; 6; 10; 18; 24; 25; 79; 171].

Despite showing the best effectiveness, safety, and tolerability of commercially available medications evaluated in patients with refractory/unexplained chronic cough patients and despite recommended by international clinical practice guidelines, use of low-dose, slow-release morphine may be untenable or unrealistic. In light of this fact, gabapentin, pregabalin, and amitriptyline remain options for effective pharmacotherapy. Clinicians should also stay informed about possible FDA approval of gafapixant, the first-ever drug approved for refractory/unexplained chronic cough in several other countries, and about phase 3 trials of campilixant. Approval of these agents could expand the treatment options for these patients and potentially improve patient quality of life.

Customer Information and Evaluation are located on pages 79–80.

# Course Availability List

These courses may be ordered by mail on the Customer Information form located on page 79.

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## TREATMENT OF HEART FAILURE: AN UPDATE

#30934 • 10 ANCC / 3 PHARM HOURS

**BOOK BY MAIL – \$68 • ONLINE – \$60**

**Purpose:** The purpose of this course is to provide nurses and ancillary nursing personnel with current information about the scientific advances in the treatment of acute heart failure.

**Audience:** This course is designed for nurses and ancillary nurse personnel involved in the treatment and continued assessment of patients with heart failure.

**Additional Approvals:** AACN Synergy CERP Category A, CCMC



## PRESSURE INJURIES AND SKIN CARE

#34344 • 5 ANCC HOURS

**BOOK BY MAIL – \$38 • ONLINE – \$30**

**Purpose:** The purpose of this course is to provide nurses with the information necessary to accurately identify, treat, and manage skin breakdown (pressure ulcers), thereby improving patient outcomes and quality of life.

**Audience:** This course is designed for nurses in all practice settings, particularly those caring for patients at high risk for developing pressure injuries.

**Additional Approvals:** AACN Synergy CERP Category A, CCMC



## OSHA AND HEALTHCARE FACILITIES

#31234 • 5 ANCC HOURS

**BOOK BY MAIL – \$38 • ONLINE – \$30**

**Purpose:** The purpose of this course is to provide information that will allow facilities to more easily comply with the broad spectrum of rules covered by the OSHA regulations.

**Audience:** This course is designed for healthcare staff in all specialties.

**Additional Approvals:** AACN Synergy CERP Category B

## DIABETIC HYPOGLYCEMIA

#34654 • 5 ANCC / 5 PHARM HOURS

**BOOK BY MAIL – \$38 • ONLINE – \$30**

**Purpose:** The purpose of this course is to provide nurses and healthcare professionals with a foundation of understanding hypoglycemia in order to assure the highest quality of care is provided to patients.

**Audience:** This course is designed for nurses in any healthcare venue and dietitians with a desire to better understand the causes, recognition, and treatment of hypoglycemia in a variety of settings.

**Additional Approvals:** AACN Synergy CERP Category A, CCMC

## BURNOUT: IMPACT ON NURSING AND QUALITY OF CARE

#31434 • 5 ANCC HOURS

**BOOK BY MAIL – \$38 • ONLINE – \$30**

**Purpose:** Given the integral relationship between work-related stress, job dissatisfaction, burnout, and patient care, properly addressing nursing burnout is essential. The purpose of this course is to provide nurses with information to identify burnout and with effective strategies to manage work-related stress and prevent burnout.

**Audience:** This course is designed for nurses and nurse practitioners at all levels and in all settings, especially oncology, palliative care, mental health, and critical care.

**Additional Approvals:** AACN Synergy CERP Category C, CCMC

## ETHICAL DECISION MAKING

#37074 • 15 ANCC HOURS

**BOOK BY MAIL – \$98 • ONLINE – \$90**

**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.

**Audience:** This course is designed for all nurses and allied healthcare professionals.

**Additional Approvals:** AACN Synergy CERP Category B, CCMC



## CHILDHOOD OBESITY: IMPACT ON HEALTH CARE

#32014 • 5 ANCC / 1 PHARM HOUR

**BOOK BY MAIL – \$38 • ONLINE – \$30**

**Purpose:** The impact of childhood obesity on an already stressed healthcare system is high and is estimated to rise as the diagnoses of comorbid conditions continue to occur at a younger age. The purpose of this course is to provide nurses with the information necessary to improve the care of children and adolescents who are overweight or obese.

**Audience:** This course is designed for nurses in all practice settings with a desire to better understand the issues facing obese children and their families and the impact of childhood obesity on national and global health care.

**Additional Approvals:** AACN Synergy CERP Category A, CCMC

## VENOUS DISEASE AND ULCERS

#38632 • 5 ANCC HOURS

**BOOK BY MAIL – \$38 • ONLINE – \$30**

**Purpose:** The purpose of this course is to enable nurses to accurately assess and treat venous disease and venous ulcers and to provide patient and family education for preventive care and lifestyle changes.

**Audience:** This course is designed for nurses in all care settings who may care for patients with venous disease or ulcers.

**Additional Approvals:** AACN Synergy CERP Category A, CCMC

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# Course Availability List (Cont'd)

## RESPIRATORY CARE: ARTIFICIAL AIRWAYS, MECHANICAL VENTILATION, AND CHEST TUBES

#38802 • 3 ANCC HOURS

BOOK BY MAIL – \$26 • ONLINE – \$18

**Purpose:** The purpose of this course is to reinforce nurses' knowledge and skills related to the care of patients with artificial airways and/or chest tubes in order to improve outcomes and patient quality of life.

**Audience:** This course is designed for nurses working in critical care and general and specialty medical-surgical units in which patients require assistance maintaining a patent airway and respiration.

**Additional Approvals:** AACN Synergy CERP Category A, CCMC

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## CARING FOR THE GERIATRIC PATIENT

#39101 • 3 ANCC HOURS

BOOK BY MAIL – \$26 • ONLINE – \$18

**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.

**Audience:** This course is designed for nurses in a variety of practice settings who work with older patients.

**Additional Approvals:** AACN Synergy CERP Category A, CCMC

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## PULMONARY EMBOLISM

#90120 • 2 ANCC / 1 PHARM HOUR

BOOK BY MAIL – \$23 • ONLINE – \$15

**Purpose:** The purpose of this course is to provide healthcare professionals with the knowledge and clinical strategies necessary to optimally triage and treatment patients with pulmonary embolism.

**Audience:** This course is designed for physicians, PAs, and nurses involved in assessing, triaging, and managing patients with suspected pulmonary embolism.

**Additional Approvals:** AACN Synergy CERP Category A

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## AGITATION, SEDATION, AND DELIRIUM IN ADULT ICU PATIENTS

#90180 • 5 ANCC / 5 PHARM HOURS

BOOK BY MAIL – \$38 • ONLINE – \$30

**Purpose:** The purpose of this course is to provide prescribers and other healthcare professionals with the knowledge and skills necessary to identify and act to avoid or address agitation, inappropriate sedation, and delirium in ICU patients.

**Audience:** This course is designed for physicians, physician assistants, and nurses involved in the care of patients in intensive care units.

**Additional Approvals:** AACN Synergy CERP Category A

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## ISCHEMIC STROKE

#90284 • 10 ANCC / 5 PHARM HOURS

BOOK BY MAIL – \$68 • ONLINE – \$60

**Purpose:** The early identification and management of the risk factors for ischemic stroke can lead to substantial health benefits and reductions in cost. However, research has documented gaps between healthcare professionals' knowledge and practice with respect to prevention, demonstrating that adherence to evidence-based or guideline-endorsed recommendations pertaining to all interventions for primary and secondary prevention are underutilized or ineffective. The purpose of this course is to provide needed information about the roles of diagnosis and screening, timely evaluation of individuals with suspected stroke, immediate treatment of stroke, and the elements of effective rehabilitation programs so that healthcare professionals may implement the necessary interventions appropriately.

**Audience:** This course is designed for physicians, nurses, and physician assistants in the primary care setting. Neurologists and other healthcare practitioners will also benefit from this course.

**Additional Approvals:** AACN Synergy CERP Category A, CCMC

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## AUTISM SPECTRUM DISORDER

#92204 • 5 ANCC / 1 PHARM HOUR

BOOK BY MAIL – \$38 • ONLINE – \$30

**Purpose:** The purpose of this course is to educate healthcare professionals about the epidemiology, diagnosis, and management of ASD. Additionally, this course will provide the information necessary to screen children seen in primary care for ASD in order to appropriately refer patients and their families for more expansive assessment and treatment referral as rapidly as possible in order to avoid unnecessary morbidity and mortality.

**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 Approvals:** AACN Synergy CERP Category A, CCMC

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## MATERNAL HEALTH DISPARITIES

#93010 • 4 ANCC HOURS

BOOK BY MAIL – \$32 • ONLINE – \$24

**Purpose:** The purpose of this course is to provide healthcare providers with the knowledge and skills necessary to improve maternal outcomes in all races, ethnicities, and marginalized groups.

**Audience:** This course is designed for all healthcare providers who may intervene to improve peripartum and postpartum health care and reduce health disparities.

**Additional Approvals:** AACN Synergy CERP Category B

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# Course Availability List (Cont'd)

## **PREDIABETES: AN OPPORTUNITY TO PREVENT DIABETES**

**#94194 • 15 ANCC / 7 PHARM HOURS**

**BOOK BY MAIL – \$98 • ONLINE – \$90**

**Purpose:** Studies have shown that diabetes can be delayed or prevented in people with prediabetes, but risk reduction relies heavily on lifestyle changes on the part of the patients, making education and counseling of vital importance. The purpose of this course is to provide healthcare professionals with the information and skills necessary to effectively deal with this common condition and learn ways to help patients make healthy lifestyle choices.

**Faculty:** Susan Semb, MSN, CDCES

**Audience:** This course is designed for nurses in adult primary care, clinical, and acute care settings, healthcare and behavioral health professionals in public health and preventive medicine settings, and health education specialists.

**Additional Approvals:** AACN Synergy CERP Category A

## **HYPERTENSION: STRATEGIES TO IMPROVE OUTCOMES**

**#94223 • 5 ANCC / 5 PHARM HOURS**

**BOOK BY MAIL – \$38 • ONLINE – \$30**

**Purpose:** The purpose of this course is to provide healthcare professionals with the information necessary to develop treatment regimens associated with optimal adherence and provide adequate patient education, counseling, and support to patients with hypertension.

**Faculty:** John J. Whyte, MD, MPH

**Audience:** This course is designed for all physicians, physician assistants, nurses, and pharmacy professionals involved in the care of patients with hypertension.

**Additional Approvals:** AACN Synergy CERP Category A, CCMC

## **INFLUENZA: A COMPREHENSIVE REVIEW**

**#94424 • 10 ANCC / 5 PHARM HOURS**

**BOOK BY MAIL – \$68 • ONLINE – \$60**

**Purpose:** The purpose of this course is to provide healthcare professionals with an updated review of influenza, including clinical aspects, public health issues, and strategies for prevention. The goals are to minimize the burden of influenza on patients and communities, prevent complications and hospitalizations, and save healthcare dollars.

**Audience:** This course is designed to help healthcare professionals and allied personnel understand influenza and their role in its prevention.

**Additional Approvals:** AACN Synergy CERP Category A, CCMC

**UPDATE**

## **CANNABINOID OVERVIEW**

**#98010 • 3 ANCC / 3 PHARM HOURS**

**BOOK BY MAIL – \$26 • ONLINE – \$18**

**Purpose:** The purpose of this course is to provide healthcare professionals in all practice settings the knowledge necessary to increase their understanding of the various cannabinoids.

**Audience:** This course is designed for healthcare professionals whose patients are taking or are interested in taking cannabinoid products.

**Additional Approvals:** AACN Synergy CERP Category A

**NEW!**

## **DIETS AND DIETARY APPROACHES TO WEIGHT LOSS**

**#98120 • 4 ANCC HOURS**

**BOOK BY MAIL – \$32 • ONLINE – \$24**

**Purpose:** The purpose of this course is to provide healthcare professionals in all practice settings the knowledge necessary to counsel patients regarding diets and dietary approaches to weight management.

**Audience:** This course is designed for all physicians, nurses, and allied professionals involved in the care of patients who are interested in exploring dietary options to weight control.

**Additional Approvals:** AACN Synergy CERP Category A

**NEW!**

## **SUPPLEMENTS FOR AGING**

**#98190 • 5 ANCC / 5 PHARM HOURS**

**BOOK BY MAIL – \$38 • ONLINE – \$30**

**Purpose:** The purpose of this course is to provide healthcare professionals in all practice settings the knowledge necessary to increase their understanding of the supplements that may be used by their older adult patients.

**Audience:** This course is designed for healthcare professionals whose older patients are taking or are interested in supplements.

**Additional Approvals:** AACN Synergy CERP Category A

**NEW!**

## **AGING AND LONG-TERM CARE**

**#99354 • 3 ANCC HOURS**

**BOOK BY MAIL – \$26 • ONLINE – \$18**

**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.

**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 Approvals:** AACN Synergy CERP Category B, CCMC

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**Please answer all of the following questions and provide your signature at the bottom of this page.**  
**Your postmark or facsimile date will be used as your completion date.**

**Please read the following questions and choose the most appropriate answer for each course completed.**

1. Was the course content new or review?
2. How much time did you spend on this activity?
3. Would you recommend this course to your peers?
4. Did the course content support the stated course objective?
5. Did the course content demonstrate the author's knowledge of the subject?
6. Was the course content free of bias?
7. Before completing the course, did you identify the necessity for education on the topic to improve your nursing practice?
8. Have you achieved all of the stated learning objectives of this course?
9. Has what you think or feel about this topic changed?
10. Did study questions throughout the course promote recall of learning objectives?
11. Did evidence-based practice recommendations assist in determining the validity or relevance of the information?
12. Are you more confident in your ability to provide nursing care after completing this course?
13. Do you plan to make changes in your nursing practice as a result of this course content?

**#99090**

3 Contact Hours

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

**#91660**

3 Contact Hours

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

**#97510**

4 Contact Hours

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

**#94820**

10 Contact Hours

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

#99090 Alzheimer Disease and Dementias: Early Detection and Care Planning – If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team? \_\_\_\_\_

#91660 Falls and Fall Prevention – If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team? \_\_\_\_\_

#97510 Intercultural Competence and Patient-Centered Care – If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team? \_\_\_\_\_

#94820 Chronic Cough in Adults – If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team? \_\_\_\_\_

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

I have read the course(s) and completed the Evaluation(s) in full.  
 I understand my postmark or facsimile date will be used as my completion date.

Signature \_\_\_\_\_

*Signature required to receive continuing education credit.*

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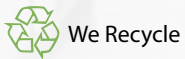
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