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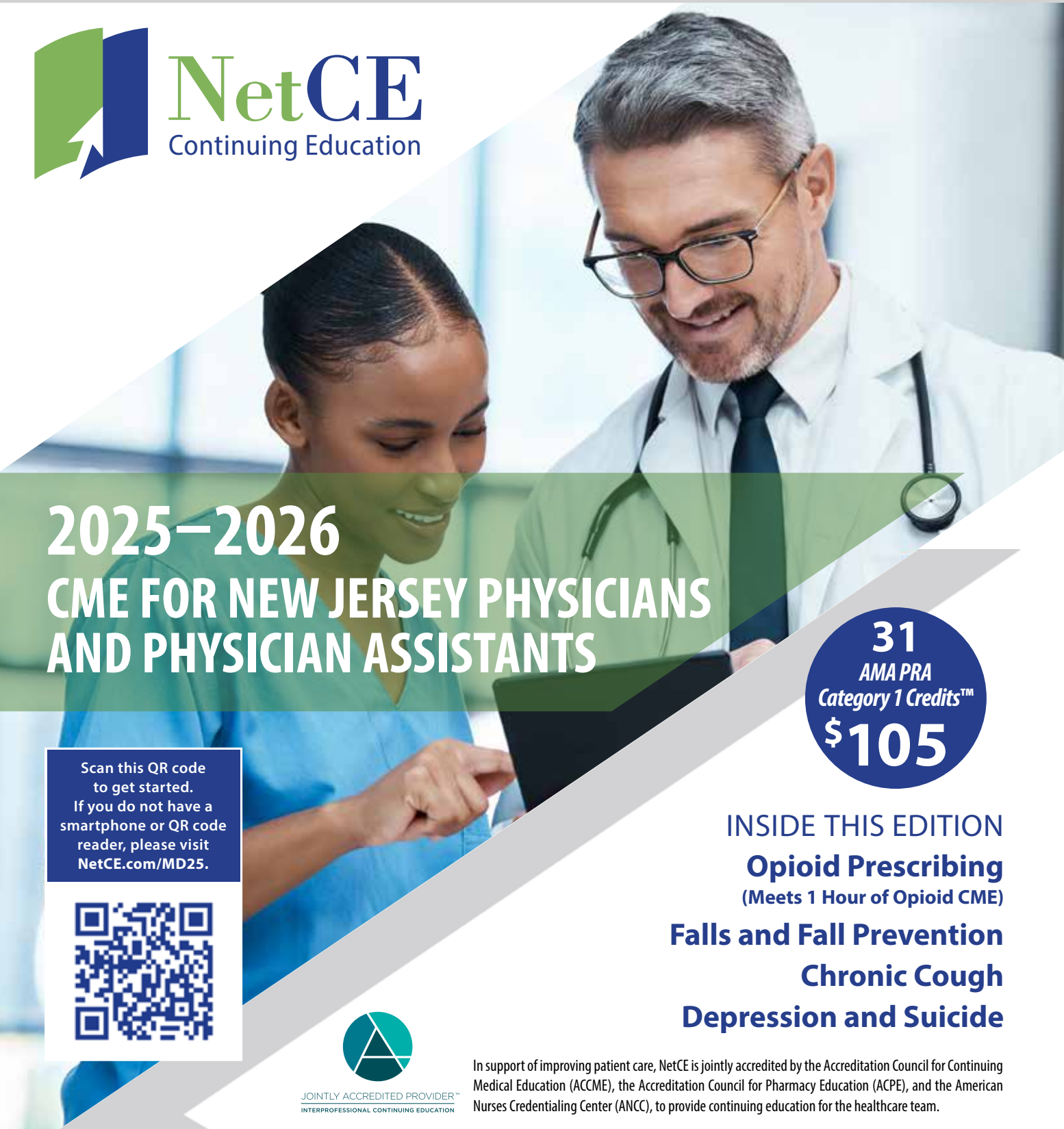

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2025–2026

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Responsible and Effective Opioid Prescribing

Special Approvals

This course meets the requirements for up to 3 hours of opioid/controlled substance/pain management/addiction education for the following states: AL, AK, AZ, AR, CA, CT, DE, GA, ID, IL, IN, IA, KS, KY, LA, MA, MD, ME, MI, MN, MS, NC, NE, NH, NJ, NM, NV, NY, RI, SC, TX, VA, VT, WA, WI, and WY.

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Audience

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

Course Objective

The purpose of this course is to provide clinicians who prescribe or distribute opioids with an appreciation for the complexities of opioid prescribing and the dual risks of litigation due to inadequate pain control and drug diversion or misuse in order to provide the best possible patient care and to prevent a growing social problem.

Learning Objectives

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

1. Apply epidemiologic trends in opioid use and misuse to current practice so at-risk patient populations can be more easily identified, assessed, and treated.
2. Create comprehensive treatment plans for patients with pain that address patient needs as well as drug diversion prevention.
3. Evaluate behaviors that may indicate drug seeking or diverting as well as approaches for patients suspected of misusing opioids.
4. Identify state and federal laws governing the proper prescription and monitoring of controlled substances.
5. Describe the available treatment modalities for opioid use disorder.

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

John M. Leonard, MD

Senior Director of Development and Academic Affairs

Sarah Campbell

Division Planner/Director Disclosure

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This activity has been approved for the American Board of Anesthesiology's® (ABA) requirements for Part II: Lifelong Learning and Self-Assessment of the American Board of Anesthesiology's (ABA) redesigned Maintenance of Certification in Anesthesiology Program® (MOCA®), known as MOCA 2.0®. Please consult the ABA website, www.theABA.org, for a list of all MOCA 2.0 requirements. Maintenance of Certification in Anesthesiology Program® and MOCA® are registered certification marks of the American Board of Anesthesiology®. MOCA 2.0® is a trademark of the American Board of Anesthesiology®.

Successful completion of this CME activity, which includes participation in the activity with individual assessments of the participant and feedback to the participant, enables the participant to earn 3 MOC points in the American Board of Pediatrics' (ABP) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABP MOC credit.

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Special Approvals

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INTRODUCTION

Pain is the leading reason for seeking medical care, and pain management is a large part of many healthcare professionals' practice. Opioid analgesics are approved by the U.S. Food and Drug Administration (FDA) for moderate and severe pain and are broadly accepted in acute pain, cancer pain, and end-of-life care, but are controversial in chronic noncancer pain. In response to the long-standing neglect of severe pain, indications for opioid analgesic prescribing were expanded in the 1990s, followed by inappropriate prescribing and increasing abuse, addiction, diversion, and overdose through the 2000s. In tandem with the continued under-treatment of pain, these practice patterns led to needless suffering from uncontrolled pain, opioid analgesic addiction, and overdose. Opioid analgesic prescribing and associated overdose peaked in 2011 with both now in multi-year decline.

Patients show substantial opioid response variations in analgesia and tolerability and may exhibit a range of psychologic, emotional, and behavioral responses that reflect inadequate pain control, an emerging opioid use problem, or both. Clinician delivery of best possible care to patients with pain requires appreciation of the complexities of opioid prescribing and the dual risks of inadequate pain control and inappropriate use, drug diversion, or overdose. A foundation for appropriate opioid prescribing is the understanding of factual data that clarify the prevalence, causality, and prevention of serious safety concerns with opioid prescribing.

SCOPE OF THE PROBLEM

Inappropriate opioid analgesic prescribing for pain is defined as the non-prescribing, inadequate prescribing, excessive prescribing, or continued prescribing despite evidence of ineffectiveness of opioids [1]. Appropriate opioid prescribing is essential to achieve pain control; to minimize patient risk of abuse, addiction, and fatal toxicity; and to minimize societal harms from diversion. The foundation of appropriate opioid prescribing is thorough patient assessment, treatment planning, and follow-up and monitoring. Essential for proper patient assessment and treatment planning is comprehension of the clinical concepts of opioid abuse and addiction, their behavioral manifestations in patients with pain, and how these potentially problematic behavioral responses to opioids both resemble and differ from physical dependence and pseudodependence. Prescriber knowledge deficit has been identified as a key obstacle to appropriate opioid prescribing and, along with gaps in policy, treatment, attitudes, and research, contributes to widespread inadequate treatment of pain [2].

The extent of opioid analgesic use in the United States in the 2000s was unprecedented in the country's history and unparalleled anywhere in the world. Before 1990, physicians in the United States were skeptical of prescribing opioids for chronic

noncancer pain. In 2019, 22.1% of adults used a prescription opioid such as oxycodone and hydrocodone for chronic pain, and sales of opioid analgesics totaled approximately $7 billion in 2016 [3; 4].

Worldwide consumption of opioid analgesics has increased dramatically in the past few decades, with the United States driving a substantial proportion of this increase. For example, the 1990 global consumption of hydrocodone was 4 tons (3,628 kg), compared with the 2009 consumption of 39 tons (35,380 kg); 99% of this was consumed in the United States. Similarly, 3 tons (2,722 kg) of oxycodone were consumed globally in 1990, versus 77 tons (69,853 kg) in 2009, of which 62 tons (56,245 kg or 81%) were consumed in the United States [5]. With only 4.23% of the world's population, the United States annually consumes more than 80% of all opioid supplies, including [6; 7]:

- 99% of all hydrocodone
- 68% of all oxycodone
- 52% of all methadone
- 40% of all hydromorphone
- 19% of all fentanyl

This disproportionate rate of opioid consumption reflects sociocultural and economic factors and standards of clinical medicine.

Between 1992 and 2003, the U.S. population increased 14%, while persons abusing opioid analgesics increased 94% and first-time non-medical opioid analgesic users 12 to 17 years of age increased 542% [8]. It is interesting to note that while opioid prescribing has increased precipitously among adults in the United States, the rate remained low and steady for children between 1996 and 2012 [9]. A study using data from 2005 to 2015 showed opioid prescribing in 57 million visits from adolescents and young adults, representing a prescribing rate of nearly 15% in emergency departments and nearly 3% in outpatient clinical settings [10]. During the course of the study, emergency department prescribing decreased slightly while outpatient clinical setting prescribing remained the same [10]. To assist in monitoring the public health problem associated with prescribed opioids, numerous governmental, non-profit, and private sector agencies and organizations are involved in collecting, reporting, and analyzing data on the abuse, addiction, fatal overdose, and treatment admissions related to opioid analgesics.

Before it was halted in 2011, the Drug Abuse Warning Network (DAWN) provided estimates of the health consequences of nonmedical use of individual drugs, including opioid medications [11]. DAWN indicates that opioid abuse is a growing problem in the United States. In 2005 and 2011, hydrocodone and its combinations accounted for 51,225 and 97,183 emergency department visits, respectively. Oxycodone and its combinations resulted in 42,810 visits to the emergency department in 2005; this number increased to 175,229 visits in 2011 [12; 13]. Visits for nonmedical use of all opioids increased from 217,594 to 420,040 during the six-year period. In 2016–2017, there were 127,101 nonmedical opioid emergency department visits [14]. While this number is an improvement from previous years, nonmedical use accounts for 47.6% of all emergency department visits related to opioids [14].

PAIN MANAGEMENT APPROACHES

Healthcare professionals should know the best clinical practices in opioid prescribing, including the associated risks of opioids, approaches to the assessment of pain and function, and pain management modalities. Pharmacologic and nonpharmacologic approaches should be used on the basis of current knowledge in the evidence base or best clinical practices. Patients with moderate-to-severe chronic pain who have been assessed and treated, over a period of time, with non-opioid therapy or nonpharmacologic pain therapy without adequate pain relief, are considered to be candidates for a trial of opioid therapy [3; 15]. Initial treatment should always be considered individually determined and as a trial of therapy, not a definitive course of treatment [16].

In 2016, the CDC issued updated guidance on the prescription of opioids for chronic pain [3]. The guideline addresses when to initiate or continue opioids for chronic pain; opioid selection, dosage, duration, follow-up, and discontinuation; and assessing risk and addressing harms of opioid use. In addition, the CDC further updated guidance against the misapplication of this guideline in 2019, noting that some policies and practices attributed to the guideline were inconsistent with the recommendations [17].

While these guidelines were based on the best available evidence at the time, there was some criticism that they were too focused on limiting opioid prescriptions—to the point of patients and prescribers complaining of stigma and reduced access to needed opioid analgesics. In response to this and to the availability of new evidence, the CDC published an updated guideline in 2022 [18]. The updated clinical practice guideline is intended to achieve improved communication between clinicians and patients about the risks and benefits of pain treatment, including opioid therapy for pain; improved safety and effectiveness for pain treatment, resulting in improved function and quality of life for patients experiencing pain; and a reduction in the risks associated with long-term opioid therapy, including opioid use disorder, overdose, and death [18]. It is important to remember that inappropriately limiting necessary opioid medications to address patients' pain can be damaging and should be avoided. A central tenet of the updated 2022 guideline is that acute, subacute, and chronic pain needs to be appropriately and effectively treated regardless of whether opioids are part of a treatment regimen [18].

ACUTE PAIN

Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids in a quantity no greater than that needed for the expected duration of severe pain. In most cases, three days or less will be sufficient; more than seven days will rarely be needed [3]. Payers and health systems should not use the 2022 guideline to set rigid standards related to dosage or duration of opioid therapy. The guideline is not a replacement for clinical judgment or individualized, patient-centered care [19].

With postoperative, acute, or intermittent pain, analgesia often requires frequent titration, and the two- to four-hour analgesic duration with short-acting hydrocodone, morphine, and oxycodone is more effective than extended-release formulations. Short-acting opioids are also recommended in patients who are medically unstable or with highly variable pain intensity [20; 21; 22].

CHRONIC PAIN

Nonpharmacologic therapy and non-opioid pharmacologic therapy are the preferred first-line therapies for chronic pain [18]. Several nonpharmacologic approaches are therapeutic complements to pain-relieving medication, lessening the need for higher doses and perhaps minimizing side effects. These interventions can help decrease pain or distress that may be contributing to the pain sensation. Approaches include palliative radiotherapy, complementary/alternative methods, manipulative and body-based methods, and cognitive/behavioral techniques. The choice of a specific nonpharmacologic intervention is based on the patient's preference, which, in turn, is usually based on a successful experience in the past.

Implantable intrathecal opioid infusion and/or spinal cord stimulation may be options for severe, intractable pain. Both options require that devices or ports be implanted, with associated risks. With intrathecal opioid infusion, the ability to deliver the drug directly into the spine provides pain relief with significantly smaller opioid doses, which can help to minimize side effects (e.g., drowsiness, dizziness, dry mouth, nausea, vomiting, and constipation) that can accompany systemic pain medications that might be delivered orally, transdermally, or through an IV [23]. However, use of opioid infusion has traditionally been limited to cancer pain. With spinal cord stimulation therapy, the most challenging aspect is patient selection. In order for patients to be considered for spinal cord stimulation, other options should have been ineffective or be contraindicated. Spinal cord stimulation is indicated for severe neuropathic pain persisting at least six months.

If opioids are used, they should be combined with nonpharmacologic therapy and non-opioid pharmacologic therapy, as appropriate. Clinicians should consider opioid therapy only if expected benefits for pain and function are anticipated to outweigh risks to the patient [18].

Opioid therapy for chronic pain should be presented as a trial for a pre-defined period (e.g., ≤30 days). The goals of treatment should be established with all patients prior to the initiation of opioid therapy, including reasonable improvements in pain, function, depression, anxiety, and avoidance of unnecessary or excessive medication use [1; 18]. The treatment plan should describe therapy selection, measures of progress, and other diagnostic evaluations, consultations, referrals, and therapies. Opioid therapy should not be initiated without consideration by the clinician and patient of an exit strategy to be used if opioid therapy is unsuccessful [18].

In patients who are opioid-naïve, start at the lowest possible dose and titrate to effect. Dosages for patients who are opioid-tolerant should always be individualized and titrated by efficacy and tolerability [1; 18]. When starting opioid therapy for chronic pain, clinicians should prescribe short-acting instead of extended-release/long-acting opioid formulations [18].

The need for frequent progress and benefit/risk assessments during the trial should be included in patient education. Patients should also have full knowledge of the warning signs and symptoms of respiratory depression. Prescribers should carefully reassess evidence of benefits and risks when increasing the dosage to ≥50 mg morphine equivalent dose (MED) per day. Decisions to titrate dose to ≥90 mg MED/day should be avoided or carefully justified [17; 18].

Prescribers should be knowledgeable of federal and state opioid prescribing regulations. Issues of equianalgesic dosing, close patient monitoring during all dose changes, and cross-tolerance with opioid conversion should be considered. If necessary, treatment may be augmented, with preference for nonopioids and immediate-release opioids over long-acting/extended-release opioids. Taper opioid dose when no longer needed [18; 24].

PALLIATIVE CARE AND PAIN AT THE END OF LIFE

Unrelieved pain is the greatest fear among people with a life-limiting disease, and the need for an increased understanding of effective pain management is well-documented [25]. Although experts have noted that 75% to 90% of end-of-life pain can be managed effectively, rates of pain are high, even among people receiving palliative care [25; 26; 27; 28].

The inadequate management of pain is the result of several factors related to both patients and clinicians. In a survey of oncologists, patient reluctance to take opioids or to report pain were two of the most important barriers to effective pain relief [29]. This reluctance is related to a variety of attitudes and beliefs [25; 29]:

- Fear of addiction to opioids
- Worry that if pain is treated early, there will be no options for treatment of future pain
- Anxiety about unpleasant side effects from pain medications

- Fear that increasing pain means that the disease is getting worse
- Desire to be a "good" patient
- Concern about the high cost of medications

Education and open communication are the keys to overcoming these barriers. Every member of the healthcare team should reinforce accurate information about pain management with patients and families. The clinician should initiate conversations about pain management, especially regarding the use of opioids, as few patients will raise the issue themselves or even express their concerns unless they are specifically asked [30]. It is important to acknowledge patients' fears individually and provide information to help them differentiate fact from fiction [26]. For example, when discussing opioids with a patient who fears addiction, the clinician should explain that the risk of addiction is low [25]. It is also helpful to note the difference between addiction and physical dependence.

There are several other ways clinicians can allay patients' fears about pain medication:

- Assure patients that the availability of pain relievers cannot be exhausted; there will always be medications if pain becomes more severe.
- Acknowledge that side effects may occur but emphasize that they can be managed promptly and safely and that some side effects will abate over time.
- Explain that pain and severity of disease are not necessarily related.

Encouraging patients to be honest about pain and other symptoms is also vital. Clinicians should ensure that patients understand that pain is multidimensional and emphasize the importance of talking to a member of the healthcare team about possible causes of pain, such as emotional or spiritual distress. The healthcare team and patient should explore psychosocial and cultural factors that may affect self-reporting of pain, such as concern about the cost of medication.

Clinicians' attitudes, beliefs, and experiences also influence pain management, with addiction, tolerance, side effects, and regulations being the most important concerns [25; 27; 29; 31]. A lack of appropriate education and training in the assessment and management of pain has been noted to be a substantial contributor to ineffective pain management [29; 31]. As a result, many clinicians, especially primary care physicians, do not feel confident about their ability to manage pain in their patients [29; 31].

Clinicians require a clear understanding of available medications to relieve pain, including appropriate dosing, safety profiles, and side effects. If necessary, clinicians should consult with pain specialists to develop an effective approach.

Strong opioids are used for severe pain at the end of life [26; 27]. Morphine, buprenorphine, oxycodone, hydromorphone, fentanyl, and methadone are the most widely used in the United States [32]. Unlike nonopioids, opioids do not have a ceiling effect, and the dose can be titrated until pain is relieved or side effects become unmanageable. For patients who are opioid-naïve or who have been receiving low doses of a weak opioid, the initial dose should be low, and, if pain persists, the dose may be titrated up daily until pain is controlled.

More than one route of opioid administration will be needed by many patients during end-of-life care, but in general, opioids should be given orally, as this route is the most convenient and least expensive. The transdermal route is preferred to the parenteral route, although dosing with a transdermal patch is less flexible and so may not be appropriate for patients with unstable pain [27]. Intramuscular injections should be avoided because injections are painful, drug absorption is unreliable, and the time to peak concentration is long [27].

CREATING A TREATMENT PLAN AND ASSESSMENT OF ADDICTION RISK

Information obtained by patient history, physical examination, and interview, from family members, a spouse, or state prescription drug monitoring program (PDMP), and from the use of screening and assessment tools can help the clinician to stratify the patient according to level of risk for developing problematic opioid behavioral responses (***Table 1***) [33; 34]. Low-risk patients receive the standard level of monitoring, vigilance, and care. Moderate-risk patients should be considered for an additional level of monitoring and provider contact, and high-risk patients are likely to require intensive and structured monitoring and follow-up contact, additional consultation with psychiatric and addiction medicine specialists, and limited supplies of short-acting opioid formulations [18; 35].

Before deciding to prescribe an opioid analgesic, clinicians should perform and document a detailed patient assessment that includes [1]:

- Pain indications for opioid therapy
- Nature and intensity of pain
- Past and current pain treatments and patient response
- Comorbid conditions
- Pain impact on physical and psychologic function
- Social support, housing, and employment
- Home environment (i.e., stressful or supportive)
- Pain impact on sleep, mood, work, relationships, leisure, and substance use
- Patient history of physical, emotional, or sexual abuse

RISK STRATIFICATION FOR PATIENTS PRESCRIBED OPIOIDS
Low Risk
Definable physical pathology with objective signs and reliable symptoms
Clinical correlation with diagnostic testing, including MRI, physical examination, and interventional diagnostic techniques
With or without mild psychologic comorbidity
With or without minor medical comorbidity
No or well-defined and controlled personal or family history of alcoholism or substance abuse
Age 45 years or older
High levels of pain acceptance and active coping strategies
High motivation and willingness to participate in multimodal therapy and attempting to function at normal levels
Medium Risk
Significant pain problems with objective signs and symptoms confirmed by radiologic evaluation, physical examination, or diagnostic interventions
Moderate psychologic problems, well controlled by therapy
Moderate coexisting medical disorders that are well controlled by medical therapy and are not affected by chronic opioid therapy (e.g., central sleep apnea)
Develops mild tolerance but not hyperalgesia without physical dependence or addiction
History of personal or family history of alcoholism or substance abuse
Pain involving more than three regions of the body
Defined pathology with moderate levels of pain acceptance and coping strategies
Willing to participate in multimodal therapy, attempting to function in normal daily life
High Risk
Widespread pain without objective signs and symptoms
Pain involving more than three regions of the body
Aberrant drug-related behavior
History of alcoholism or drug misuse, abuse, addiction, diversion, dependency, tolerance, or hyperalgesia
Major psychologic disorders
Age younger than 45 years
HIV-related pain
High levels of pain exacerbation and low levels of coping strategies
Unwilling to participate in multimodal therapy, not functioning close to a near normal lifestyle
HIV = human immunodeficiency syndrome, MRI = magnetic resonance imaging.
Source: [33; 34] *Table 1*

If substance abuse is active, in remission, or in the patient's history, consult an addiction specialist before starting opioids [1]. In active substance abuse, do not prescribe opioids until the patient is engaged in treatment/recovery program or other arrangement made, such as addiction professional co-management and additional monitoring. When considering an opioid analgesic (particularly those that are extended-release or long-acting), one must always weigh the benefits against the risks of overdose, abuse, addiction, physical dependence and tolerance, adverse drug interactions, and accidental exposure by children [18; 24].

Screening and assessment tools can help guide patient stratification according to risk level and inform the appropriate degree of structure and monitoring in the treatment plan. It should be noted that despite widespread endorsement of screening tools used to help determine patient risk level, most tools have not been extensively evaluated, validated, or compared to each other, and evidence of their reliability is poor [33; 34].

RISK ASSESSMENT TOOLS

Opioid Risk Tool (ORT)

The Opioid Risk Tool (ORT) is a five-item, patient-administered assessment to help predict aberrant drug-related behavior. The ORT is also used to establish patient risk level through categorization into low, medium, or high levels of risk for aberrant drug-related behaviors based on responses to questions of previous alcohol/drug abuse, psychologic disorders, and other risk factors [36].

Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R)

The Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R) is a patient-administered, 24-item screen with questions addressing history of alcohol/substance use, psychologic status, mood, cravings, and stress. Like the ORT, the SOAPP-R helps assess risk level of aberrant drug-related behaviors and the appropriate extent of monitoring [36; 37].

Screening Instrument or Substance Abuse Potential (SISAP)

The Screening Instrument or Substance Abuse Potential (SISAP) tool is a self-administered, five-item questionnaire addressing history developed used to predict the risk of opioid misuse. The SISAP is used to identify patients with a history of alcohol/substance abuse and improve pain management by facilitating focus on the appropriate use of opioid analgesics and therapeutic outcomes in the majority of patients who are not at risk of opioid abuse, while carefully monitoring those who may be at greater risk [36].

CAGE and CAGE-AID

The original CAGE (Cut down, Annoyed, Guilty, and Eye-opener) Questionnaire consisted of four questions designed to help clinicians determine the likelihood that a patient was misusing or abusing alcohol. These same four questions were modified to create the CAGE-AID (adapted to include drugs), revised to assess the likelihood of current substance abuse [38].

Diagnosis, Intractability, Risk, and Efficacy (DIRE) Score

The Diagnosis, Intractability, Risk, and Efficacy (DIRE) risk assessment score is a clinician-rated questionnaire that is used to predict patient compliance with long-term opioid therapy [36; 39]. Patients scoring lower on the DIRE tool are poor candidates for long-term opioid analgesia.

INFORMED CONSENT AND TREATMENT AGREEMENTS

The initial opioid prescription is preceded by a written informed consent or "treatment agreement" [1]. This agreement should address potential side effects, tolerance and/or physical dependence, drug interactions, motor skill impairment, limited evidence of long-term benefit, misuse, dependence, addiction, and overdose. Informed consent documents should include information regarding the risk/benefit profile for the drug(s) being prescribed. The prescribing policies should be clearly delineated, including the number/frequency of refills, early refills, and procedures for lost or stolen medications.

The treatment agreement also outlines joint physician and patient responsibilities. The patient agrees to using medications safely, refraining from "doctor shopping," and consenting to routine urine drug testing (UDT). The prescriber's responsibility is to address unforeseen problems and prescribe scheduled refills. Reasons for opioid therapy change or discontinuation should be listed. Agreements can also include sections related to follow-up visits, monitoring, and safe storage and disposal of unused drugs.

PERIODIC REVIEW AND MONITORING

When implementing a chronic pain treatment plan that involves the use of opioids, the patient should be frequently reassessed for changes in pain origin, health, and function [1]. This can include input from family members and/or the state PDMP. During the initiation phase and during any changes to the dosage or agent used, patient contact should be increased. At every visit, chronic opioid response may be monitored according to the "5 A's" [1; 40]:

- Analgesia
- Activities of daily living
- Adverse or side effects
- Aberrant drug-related behaviors
- Affect (i.e., patient mood)

Signs and symptoms that, if present, may suggest a problematic response to the opioid and interference with the goal of functional improvement include [41; 42]:

- Excessive sleeping or days and nights turned around
- Diminished appetite
- Short attention span or inability to concentrate
- Mood volatility, especially irritability
- Lack of involvement with others
- Impaired functioning due to drug effects
- Use of the opioid to regress instead of re-engaging in life
- Lack of attention to hygiene and appearance

The decision to continue, change, or terminate opioid therapy is based on progress toward treatment objectives and absence of adverse effects and risks of overdose or diversion [1]. Satisfactory therapy is indicated by improvements in pain, function, and quality of life. Brief assessment tools to assess pain and function may be useful, as may UDTs. Treatment plans may include periodic pill counts to confirm adherence and minimize diversion.

Involvement of Family

Family members of the patient can provide the clinician with valuable information that better informs decision making regarding continuing opioid therapy. Family members can observe whether a patient is losing control of his or her life or becoming less functional or more depressed during the course of opioid therapy. They can also provide input regarding positive or negative changes in patient function, attitude, and level of comfort. The following questions can be asked of family members or a spouse to help clarify whether the patient's response to opioid therapy is favorable or unfavorable [41; 42]:

- Is the person's day centered around taking the opioid medication? Response can help clarify long-term risks and benefits of the medication and identify other treatment options.
- Does the person take pain medication only on occasion, perhaps three or four times per week? If yes, the likelihood of addiction is low.

- Have there been any other substance (alcohol or drug) abuse problems in the person's life? An affirmative response should be taken into consideration when prescribing.
- Does the person in pain spend most of the day resting, avoiding activity, or feeling depressed? If so, this suggests the pain medication is failing to promote rehabilitation. Daily activity is essential, and the patient may be considered for enrollment in a graduated exercise program
- Is the person in pain able to function (e.g., work, do household chores, play) with pain medication in a way that is clearly better than without? If yes, this suggests the pain medication is contributing to wellness.

Assessment Tools

VIGIL

VIGIL is the acronym for a five-step risk management strategy designed to empower clinicians to appropriately prescribe opioids for pain by reducing regulatory concerns and to give pharmacists a framework for resolving ambiguous opioid analgesic prescriptions in a manner that preserves legitimate patient need while potentially deterring diverters. The components of VIGIL are:

- Verification: Is this a responsible opioid user?
- Identification: Is the identity of this patient verifiable?
- Generalization: Do we agree on mutual responsibilities and expectations?
- Interpretation: Do I feel comfortable allowing this person to have controlled substances?
- Legalization: Am I acting legally and responsibly?
- The foundation of VIGIL is a collaborative physician/pharmacist relationship [43].

Current Opioid Misuse Measure (COMM)

The Current Opioid Misuse Measure (COMM) is a 17-item patient self-report assessment designed to help clinicians identify misuse or abuse in patients being treated for chronic pain. Unlike the ORT and the SOAPP-R, the COMM identifies aberrant behaviors associated with opioid misuse in patients already receiving long-term opioid therapy [35]. Sample questions include: In the past 30 days, how often have you had to take more of your medication than prescribed? In the past 30 days, how much of your time was spent thinking about opioid medications (e.g., having enough, taking them, dosing schedule)?

Pain Assessment and Documentation Tool (PADT)

Guidelines by the CDC, the Federation of State Medical Boards (FSMB), and the Joint Commission stress the importance of documentation from both a healthcare quality and medicolegal perspective. Research has found widespread deficits in chart notes and progress documentation with patients with chronic pain receiving opioid therapy, and the Pain Assessment and Documentation Tool (PADT) was designed to address these shortcomings [44]. The PADT is a clinician-directed interview, with most sections (e.g., analgesia, activities of daily living, adverse events) consisting of questions asked of the patient. However, the potential aberrant drug-related behavior section must be completed by the physician based on his or her observations of the patient.

The Brief Intervention Tool

The Brief Intervention Tool is a 26-item, "yes-no," patient-administered questionnaire used to identify early signs of opioid abuse or addiction. The items assess the extent of problems related to drug use in several areas, including drug use-related functional impairment [45].

Urine Drug Tests

UDTs may be used to monitor adherence to the prescribed treatment plan and to detect unsanctioned drug use. They should be used more often in patients receiving addiction therapy, but clinical judgment is the ultimate guide to testing frequency (***Table 2***) [46]. The CDC 2016 guideline recommends clinicians should use UDT before starting opioid therapy and consider UDT at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs [3]. However, this recommendation was based on low-quality evidence that indicates little confidence in the effect estimate, and it is not included in the 2022 updated guideline [18].

Initially, testing involves the use of class-specific immunoassay drug panels [1]. If necessary, this may be followed with gas chromatography/mass spectrometry for specific drug or metabolite detection. It is important that testing identifies the specific drug rather than the drug class, and the prescribed opioid should be included in the screen. Any abnormalities should be confirmed with a laboratory toxicologist or clinical pathologist. Immunoassay may be used point-of-care for "on-the-spot" therapy changes, but the high error rate prevents its use in major clinical decisions except with liquid chromatography coupled to tandem mass spectrometry confirmation.

Urine test results suggesting opioid misuse should be discussed with the patient using a positive, supportive approach. The test results and the patient discussion should be documented.

CONCURRENT USE OF BENZODIAZEPINES

In 2021, nearly 14% of persons who died of an opioid overdose also tested positive for benzodiazepines, a class of sedative medication commonly prescribed for anxiety, insomnia, panic attack, and muscle spasm [47]. Benzodiazepines work by raising the level of the neurotransmitter gamma-aminobutyric acid (GABA) in the brain. Common formulations include diazepam, alprazolam, and clonazepam. Combining benzodiazepines with opioids is unsafe because both classes of drug cause central nervous system depression and sedation and

PATIENT RISK LEVEL AND FREQUENCY OF MONITORING			
Monitoring Tool	**Patient Risk Level**		
	Low	**Medium**	**High**
Urine drug test	Every 1 to 2 years	Every 6 to 12 months	Every 3 to 6 months
State prescription drug monitoring program	Twice per year	Three times per year	Four times per year
Source: [46]			*Table 2*

can decrease respiratory drive—the usual cause of overdose fatality. Both classes have the potential for drug dependence and addiction.

The CDC recommends that healthcare providers use caution when prescribing benzodiazepines concurrently with opioids whenever possible [18]. If a benzodiazepine is to be discontinued, the clinician should taper the medication gradually, because abrupt withdrawal can lead to rebound anxiety and complications such as hallucinations, seizures, delirium tremens, and, in rare instances, death. The rate of tapering should be individualized [18].

CONSULTATION AND REFERRAL

It is important to seek consultation or patient referral when input or care from a pain, psychiatry, addiction, or mental health specialist is necessary. Clinicians who prescribe opioids should become familiar with opioid addiction treatment options (including licensed opioid treatment programs for methadone and office-based opioid treatment for buprenorphine) if referral is needed [1].

Ideally, providers should be able to refer patients with active substance abuse who require pain treatment to an addiction professional or specialized program. In reality, these specialized resources are scarce or non-existent in many areas [1]. Therefore, each provider will need to decide whether the risks of continuing opioid treatment while a patient is using illicit drugs outweigh the benefits to the patient in terms of pain control and improved function [48].

MEDICAL RECORDS

As noted, documentation is a necessary aspect of all patient care, but it is of particular importance when opioid prescribing is involved. All clinicians should maintain accurate, complete, and up-to-date medical records, including all written or telephoned prescription orders for opioid analgesics and other controlled substances, all written instructions to the patient for medication use, and the name, telephone number, and address of the patient's pharmacy [1]. Good medical records demonstrate that a service was provided to the patient and that the service was medically necessary. Regardless of the treatment outcome, thorough medical records protect the prescriber.

PATIENT EDUCATION ON THE USE AND DISPOSAL OF OPIOIDS

Patients and caregivers should be counseled regarding the safe use and disposal of opioids. As part of its mandatory Risk Evaluation and Mitigation Strategy (REMS) for extended-release/long-acting opioids, the U.S. Food and Drug Administration (FDA) has developed a patient counseling guide with information on the patient's specific medications, instructions for emergency situations and incomplete pain control, and warnings not to share medications or take them unprescribed [49; 50].

When prescribing opioids, clinicians should provide patients with the following information [49]:

- Product-specific information
- Taking the opioid as prescribed
- Importance of dosing regimen adherence, managing missed doses, and prescriber contact if pain is not controlled
- Warning and rationale to never break or chew/crush tablets or cut or tear patches prior to use
- Warning and rationale to avoid other central nervous system depressants, such as sedative-hypnotics, anxiolytics, alcohol, or illicit drugs
- Warning not to abruptly halt or reduce the opioid without physician oversight of safe tapering when discontinuing
- The potential of serious side effects or death
- Risk factors, signs, and symptoms of overdose and opioid-induced respiratory depression, gastrointestinal obstruction, and allergic reactions
- The risks of falls, using heavy machinery, and driving
- Warning and rationale to never share an opioid analgesic
- Rationale for secure opioid storage
- Warning to protect opioids from theft
- Instructions for disposal of unneeded opioids, based on product-specific disposal information

There are no universal recommendations for the proper disposal of unused opioids, and patients are rarely advised of what to do with unused or expired medications [51]. According to the FDA, most medications that are no longer necessary or have expired should be removed from their containers, mixed with undesirable substances (e.g., cat litter, used coffee grounds), and put into an impermeable, nondescript container (e.g., disposable container with a lid or a sealed bag) before throwing in the trash [52]. Any personal information should be obscured or destroyed. The FDA recommends that certain medications, including oxycodone/acetaminophen (Percocet), oxycodone (OxyContin tablets), and transdermal fentanyl (Duragesic Transdermal System), be flushed down the toilet instead of thrown in the trash [52; 53]. The FDA provides a free toolkit of materials (e.g., social media images, fact sheets, posters) to raise awareness of the serious dangers of keeping unused opioid pain medicines in the home and with information about safe disposal of these medicines. The Remove the Risk Outreach toolkit is updated regularly and can be found at https://www.fda.gov/drugs/ensuring-safe-use-medicine/safe-opioid-disposal-remove-risk-outreach-toolkit [53]. Patients should be advised to flush prescription drugs down the toilet only if the label or accompanying patient information specifically instructs doing so. In April 2023, the FDA issued a letter requiring all manufacturers of opioid analgesics dispensed in outpatient settings to submit a proposed modification to the Opioid Analgesic REMS. The modification requires manufacturers to make available prepaid mail-back envelopes to outpatient pharmacies and other opioid dispensers as an opioid analgesic disposal option for patients. The FDA expects to take action on this modification in 2024 [50].

The American College of Preventive Medicine has established best practices to avoid diversion of unused drugs and educate patients regarding drug disposal [51]:

- Consider writing prescriptions in smaller amounts.
- Educate patients about safe storing and disposal practices.
- Give drug-specific information to patients about the temperature at which they should store their medications. Generally, the bathroom is not the best storage place. It is damp and moist, potentially resulting in potency decrements, and accessible to many people, including children and teens, resulting in potential theft or safety issues.
- Ask patients not to advertise that they are taking these types of medications and to keep their medications secure.
- Refer patients to community "take back" services overseen by law enforcement that collect controlled substances, seal them in plastic bags, and store them in a secure location until they can be incinerated. Contact your state law enforcement agency or visit https://www.dea.gov to determine if a program is available in your area.

DISCONTINUING OPIOID THERAPY

The decision to continue or end opioid prescribing should be based on a physician-patient discussion of the anticipated benefits and risks. An opioid should be discontinued with resolution of the pain condition, intolerable side effects, inadequate analgesia, lack of improvement in quality of life despite dose titration, deteriorating function, or significant aberrant medication use [1; 18].

Clinicians should provide patients physically dependent on opioids with a safely structured tapering protocol. Withdrawal is managed by the prescribing physician or referral to an addiction specialist. Patients should be reassured that opioid discontinuation is not the end of treatment; continuation of pain management will be undertaken with other modalities through direct care or referral.

As a side note, cannabis use by patients with chronic pain receiving opioid therapy has traditionally been viewed as a treatment agreement violation that is grounds for termination of opioid therapy. However, some now argue against cannabis use as a rationale for termination or substantial treatment and monitoring changes, especially considering the increasing legalization of medical use at the state level [48].

CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

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

IDENTIFICATION OF DRUG DIVERSION/SEEKING BEHAVIORS

Research has more closely defined the location of prescribed opioid diversion into illicit use in the supply chain from the manufacturer to the distributor, retailer, and the end user (the pain patient). This information carries with it substantial public policy and regulatory implications. The 2021 National Survey on Drug Use and Health asked non-medical users of

prescription opioids how they obtained their most recently used drugs [54]. Among persons 12 years of age or older, 33.9% obtained their prescription opioids from a friend or relative for free, 39.3% got them through a prescription from one doctor (vs. 34.7% in 2019), 7.3% bought them from a friend or relative, and 3.7% took them from a friend or relative without asking [54]. Other sources included a drug dealer or other stranger (7.9%); multiple doctors (3.2%); and theft from a doctor's office, clinic, hospital, or pharmacy (0.7%) (vs. 0.9% in 2019) [54].

As discussed, UDTs can give insight into patients who are misusing opioids. A random sample of UDT results from 800 patients treated for pain at a Veterans Affairs facility found that 25.2% were negative for the prescribed opioid while 19.5% were positive for an illicit drug/unreported opioid [55]. Negative UDT results for the prescribed opioid do not necessarily indicate diversion but may indicate the patient halted his/her use due to side effects, lack of efficacy, or pain remission. The concern arises over the increasingly stringent climate surrounding clinical decision-making regarding aberrant UDT results and that a negative result for the prescribed opioid or a positive UDT may serve as the pretense to terminate a patient rather than guide him/her into addiction treatment or an alternative pain management program [56].

In addition to aberrant urine screens, there are certain behaviors that are suggestive of an emerging opioid use disorder. The most suggestive behaviors are [48; 57; 58]:

- Selling medications
- Prescription forgery or alteration
- Injecting medications meant for oral use
- Obtaining medications from nonmedical sources
- Resisting medication change despite worsening function or significant negative effects
- Loss of control over alcohol use
- Using illegal drugs or non-prescribed controlled substances
- Recurrent episodes of:
  - Prescription loss or theft
  - Obtaining opioids from other providers in violation of a treatment agreement
  - Unsanctioned dose escalation
  - Running out of medication and requesting early refills

Behaviors with a lower level of evidence for their association with opioid misuse include [48; 57; 58]:

- Aggressive demands for more drug
- Asking for specific medications
- Stockpiling medications during times when pain is less severe
- Using pain medications to treat other symptoms
- Reluctance to decrease opioid dosing once stable
- In the earlier stages of treatment:
  - Increasing medication dosing without provider permission
  - Obtaining prescriptions from sources other than the pain provider
  - Sharing or borrowing similar medications from friends/family

INTERVENTIONS FOR SUSPECTED OR KNOWN ADDICTION OR DRUG DIVERSION

There are a number of actions that prescribers and dispensers can take to prevent or intervene in cases of drug diversion. These actions can be generally categorized based on the various mechanisms of drug diversion.

Prevention is the best approach to addressing drug diversion. As noted, a common source of nonmedical use of prescribed opioids is from a family member or friend, through sharing, buying, or stealing. To avoid drug sharing among patients, healthcare professionals should educate patients on the dangers of sharing opioids and stress that "doing prescription drugs" is the same as "using street drugs" [51]. In addition, patients should be aware of the many options available to treat chronic pain aside from opioids. To prevent theft, patients should be advised to keep medications in a private place and to refrain from telling others about the medications being used.

Communication among providers and pharmacies can help to avoid inappropriate attainment of prescription drugs through "doctor shopping." Prescribers should keep complete and up-to-date records for all controlled substance prescribing. When possible, electronic medical records should be integrated between pharmacies, hospitals, and managed care organizations [51]. If available, it is also best practice to periodically request a report from the state's prescription reporting program to evaluate the prescribing of opioids to your patients by other providers [51].

When dealing with patients suspected of drug seeking/diversion, first inquire about prescription, over-the-counter, and illicit drug use and perform a thorough examination [51]. Pill counting and/or UDT may be necessary to investigate possible drug misuse. Photo identification or other form of identification and social security number may be required prior to dispensing the drug, with proof of identity documented fully. If a patient is displaying suspicious behaviors, consider prescribing for limited quantities [59].

If a patient is found to be abusing prescribed opioids, this is considered a violation of the treatment agreement and the clinician must make the decision whether or not to continue the therapeutic relationship. If the relationship is terminated, it must be done ethically and legally. The most significant issue is the risk of patient abandonment, which is defined as ending a relationship with a patient without consideration of continuity of care and without providing notice to the patient. The American Medical Association Code of Ethics states that physicians have an obligation to support continuity of care for their patients. While physicians have the option of withdrawing from a case, they should notify the patient (or authorized decision maker) long enough in advance to permit the patient to secure another physician and facilitate transfer of care when appropriate [60]. Patients may also be given resources and/or recommendations to help them locate a new clinician.

Patients with chronic pain found to have an ongoing substance abuse problem or addiction should be referred to a pain specialist for continued treatment. Theft or loss of controlled substances is reported to the DEA. If drug diversion has occurred, the activity should be documented and a report to law enforcement should be made [59].

COMPLIANCE WITH STATE AND FEDERAL LAWS

In response to the rising incidence in prescription opioid abuse, addiction, diversion, and overdose since the late 1990s, the FDA has mandated opioid-specific REMS to reduce the potential negative patient and societal effects of prescribed opioids [50]. Other elements of opioid risk mitigation include FDA partnering with other governmental agencies, state professional licensing boards, and societies of healthcare professionals to help improve prescriber knowledge of appropriate and safe opioid prescribing and safe home storage and disposal of unused medication [41].

Several regulations and programs at the state level have been enacted in an effort to reduce prescription opioid abuse, diversion, and overdose, including [61]:

- Physical examination required prior to prescribing
- Tamper-resistant prescription forms
- Pain clinic regulatory oversight
- Prescription limits
- Prohibition from obtaining controlled substance prescriptions from multiple providers
- Patient identification required before dispensing
- Immunity from prosecution or mitigation at sentencing for individuals seeking assistance during an overdose

CONTROLLED SUBSTANCES LAWS/RULES

The U.S. Drug Enforcement Administration (DEA) is responsible for formulating federal standards for the handling of controlled substances. In 2011, the DEA began requiring every state to implement electronic databases that track prescribing habits, referred to as PDMPs. Specific policies regarding controlled substances are administered at the state level [62].

According to the DEA, drugs, substances, and certain chemicals used to make drugs are classified into five distinct categories or schedules depending upon the drug's acceptable medical use and the drug's abuse or dependency potential [63]. The abuse rate is a determinate factor in the scheduling of the drug; for example, Schedule I drugs are considered the most dangerous class of drugs with a high potential for abuse and potentially severe psychologic and/or physical dependence.

STATE-SPECIFIC LAWS AND RULES

Most states have established laws and rules governing the prescribing and dispensing of opioid analgesics. It is each prescriber's responsibility to have knowledge of and adhere to the laws and rules of the state in which he or she prescribes.

MANAGEMENT OF OPIOID USE DISORDER

Management of opioid dependence entails different methods to achieve different goals, depending on the health situation and treatment history of the patient. These treatment approaches include [64]:

- Crisis intervention: Directed at immediate survival by reversing the potentially lethal effects of overdose with an opioid antagonist.
- Harm reduction: Intended to reduce morbidity and mortality associated with use of dirty needles and overdose.
- Detoxification/withdrawal: Aims to remove the opioid of abuse from the patient's body, either through gradual taper and substitution of a long-acting opioid or through ultra-rapid opioid detoxification.
- Maintenance treatment or opioid (agonist) replacement therapy: Aimed at reduction/elimination of illicit opioid use and lifestyle stabilization. Maintenance follows detoxification/withdrawal, whereby the patient is tapered from short-acting opioids and introduced to a long-acting opioid agonist, such as methadone or buprenorphine. Patients remain on agonist therapy short-term, long-term, or indefinitely depending on individual needs.
- Abstinence-oriented therapy: Treatment directed at cure. The patient is tapered off of short-acting opioids during the detoxification/withdrawal process and may be placed on an opioid antagonist with the goal of minimizing relapse.

All treatment approaches share the common goal of improving health outcomes and reducing drug-related criminality and public nuisance [64].

CRISIS INTERVENTION

In response to acute overdose, the short-acting opioid antagonist naloxone is considered the criterion standard. Naloxone is effective in reversing respiratory depression and coma in patients who have overdosed. There is no evidence that subcutaneous or intramuscular use is inferior to intravenous naloxone. This prompted discussion of making naloxone available to the general public for administration outside the healthcare setting to treat acute opioid overdose, and in 2014, the FDA approved naloxone as an autoinjector dosage form for home use by family members or caregivers [65]. The autoinjector delivers 0.4 mg naloxone intramuscularly or subcutaneously. The autoinjector comes with visual and voice instruction, including directs to seek emergency medical care after use [65]. In 2015, the FDA approved intranasal naloxone after a fast-track designation and priority review. Intranasal naloxone is indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. It is available in a ready-to-use 2-mg, 4-mg, or 8-mg single-dose sprayer [66; 67; 68]. In 2023, the FDA approved Narcan, the first over-the-counter naloxone nasal spray [69]. Narcan is available as a 3-, 4-, or 8-mg single dose, administered in one nostril [70].

HARM REDUCTION

Harm reduction measures are primarily employed to minimize the morbidity and mortality from opioid abuse and to reduce public nuisance [38; 71]. As a part of this effort, measures to prevent and minimize the frequency and severity of overdoses have been identified. Enrollment in opioid substitution therapy, with agents such as methadone and buprenorphine, substantially reduces the risk of overdose as well as the risk for infection and other sequelae of illicit opioid use [38; 71].

DETOXIFICATION AND WITHDRAWAL

The process of tapering patients with opioid dependence from agonist therapy is often referred to as detoxification, or more accurately, medically supervised withdrawal [72; 73]. Its purpose is to eliminate physical dependence on opioid medications. It can be considered the medically supported transition to a medication-free state or to antagonist therapy. A careful and thorough review of the risks and benefits of detoxification should be provided, and informed consent obtained from patients prior to choosing this option [73; 74]. Detoxification alone should not be considered a treatment and should only be promoted in the context of a well-planned relapse-prevention program [64; 73]. Studies have shown that most patients with opioid use disorder who undergo medically supervised withdrawal will start using opioids again and will not continue in recommended care [75; 76; 77; 78; 79].

Discontinuation of opioid use must be implemented slowly and cautiously to avoid a marked abstinence syndrome. Withdrawal symptoms may not begin for days after abrupt discontinuation of methadone or buprenorphine given their longer half-lives. Protracted abstinence, or post-acute withdrawal, may last for several months and is characterized by asthenia, depression, and hypotension. Post-acute withdrawal is more likely to occur with methadone than other opioids [72].

The three primary treatment modalities used for detoxification are opioid agonists, non-opioid medications, and rapid and ultra-rapid opioid detoxification [72]. The most frequently employed method of opioid withdrawal is a slow, supervised detoxification during which an opioid agonist, usually methadone, is substituted for the abused opioid [80]. Methadone is the most frequently used opioid agonist due to the convenience of its once-a-day dosing [72]. Methadone is highly bound to plasma proteins and accumulates more readily than heroin in all body tissues. Methadone also has a longer half-life, approximately 22 hours, which makes withdrawal more difficult than from heroin. Substitution therapy with methadone has a high initial dropout rate (30% to 90%) and an early relapse rate. Alternative pharmacologic detoxification choices include clonidine (with or without methadone), midazolam, trazodone, or buprenorphine [80]. Naltrexone is used following medically supervised withdrawal to help prevent relapse to opioid misuse [81].

Many opioid withdrawal symptoms, such as restlessness, rhinorrhea, lacrimation, diaphoresis, myosis, piloerection, and cardiovascular changes, are mediated through increased sympathetic activation, the result of increased neuron activity in the locus coeruleus. Non-opioid agents (such as clonidine), which inhibit hyperactivation of noradrenergic pathways stemming from the locus coeruleus nucleus, have been used to manage acute withdrawal [80; 82]. The first non-opioid treatment approved for the management of opioid withdrawal symptoms is lofexidine [83]. In studies, lofexidine resulted in less severe withdrawal symptoms and greater treatment retention than placebo.

However, some withdrawal symptoms, including anxiety and myalgias, are resistant to clonidine; benzodiazepines and nonsteroidal anti-inflammatory agents may be necessary to treat these symptoms. To mitigate withdrawal symptoms and assist in detoxification, alpha2-agonists, opioid agonist-antagonists, benzodiazepines, and antidepressants have been used [80].

Following detoxification, patients may feel exhausted and weak. Other complications, such as slight variations in hemodynamic status and gastrointestinal tract symptoms, follow quickly and may take several days to resolve. Muscle cramps and low back pain can be treated with nonsteroidal anti-inflammatory drugs. However, the newer cyclooxygenase-2 (COX-2) inhibitors may be advantageous because they produce fewer gastrointestinal side effects [80]. Insomnia is a frequent aspect of acute and protracted withdrawal, as opioids disrupt the normal sleep-wake cycle and many addicts require narcotics to sleep. Although

long-term disruption of the normal sleep-wake cycle cannot be corrected rapidly, melatonin (3 mg), benzodiazepines, or antihistamines can be used with beneficial effects. Hypnosis and relaxation techniques are nonpharmacologic methods that may also be used [80]. Psychosocial treatments offered in addition to pharmacologic detoxification treatments positively impact treatment retention and completion, results at follow-up, and compliance [84; 85].

Ultra-Rapid Opioid Detoxification

Ultra-rapid opioid detoxification (UROD) has been developed as a means of avoiding the physical symptoms of withdrawal from opioids through the use of general anesthesia. UROD consists of naltrexone-assisted detoxification under heavy sedation or full anesthesia. UROD is also referred to as rapid or anesthesia-assisted detoxification. Other novel names for the process include [86]:

- UROD: General anesthesia; duration <6 hours
- Rapid opioid detoxification (ROD): Deep sedation; duration 6 to 72 hours
- Compressed opioid detoxification (COD) and naltrexone-compressed opioid detoxification (NCOD): Duration three to six days; preceded by a period of abstinence from opioids under sedation prior to introduction of naltrexone

The common underlying themes in all UROD techniques are a desire to condense the detoxification process into a shorter period to blunt the awareness of physical discomfort and to shorten the time lag between a patient's last dose of opioid and transfer to naltrexone maintenance [86]. This is accomplished by precipitating withdrawal following the administration of opioid antagonists under deep sedation or anesthesia.

Detoxification and withdrawal are rarely complete following UROD, and residual withdrawal symptoms can include drug craving, sympathetic hyperactivity, muscle pain, bone pain, nausea, vomiting, diarrhea, and insomnia. UROD does little to prevent protracted abstinence syndrome, which can last 3 to 10 weeks. Naltrexone may reduce opioid craving during the post-UROD period, with 50 mg per day recommended for relapse prevention. However, patients undergoing long-term naltrexone therapy can become sensitized to opioid drugs, heightening the risk of fatal overdose if opioid use is resumed [80].

A major shortcoming of UROD is the lack of evidence that an opioid antagonist can accelerate the restoration of neurobiologic homeostasis following opioid withdrawal [86]. Although significant drawbacks and questionable long-term efficacy exist with UROD, popular demand has proven difficult to restrain, in part due to the marketing of the procedure as a painless cure for opioid dependence. Marketing and the media have also blurred the fact that the original purpose of the procedure was to induce patients as rapidly as possible onto naltrexone and not to immediately permanently terminate years of opioid dependence [87].

Serious adverse events related to the anesthetic procedure also have been reported. A randomized, controlled trial directly comparing naltrexone-assisted detoxification with and without full anesthesia clearly stated that heavy sedation or full anesthesia should not be used because it does not confer any advantages in withdrawal symptom severity or increased rates of initiation or maintenance and it increases the potential for life-threatening adverse events [64]. A trial comparing naltrexone-induced, anesthesia-assisted detoxification with buprenorphine- or clonidine-assisted detoxification found no difference in withdrawal severity and rates of completion. However, potentially life-threatening adverse events associated with the UROD anesthesia were observed [88]. The risk for adverse events, the high monetary cost, and use of scarce intensive care resources suggest that this form of treatment should not be pursued [89; 90]. Additionally, UROD has not undergone the processes of therapeutic protocols, which are recognized as essential in scientific medicine, and no animal studies have been conducted with the procedure [87].

AGONIST REPLACEMENT OR ABSTINENCE THERAPY

Two principle treatment modalities are offered for patients with opioid dependence: agonist maintenance or detoxification followed by outpatient or residential drug-free treatment. Both can be effective, with no clear indication for each, although agonist maintenance leads to greater treatment retention [91]. A reasonable approach is initial outpatient or residential treatment referral for patients relatively new to treatment, with agonist maintenance appropriate for patients with history of treatment failures, greater disease severity, or a history of drug overdoses. Naltrexone is best reserved for patients with strong legal incentives to abstain, family involvement to monitor treatment, or concurrent enrollment and involvement in a psychosocial intervention [92].

At present, there are no direct interventions that are capable of reversing the effects of drugs of dependence on learning and motivation systems [93]. Instead, the management of opioid dependence often consists of pharmacotherapy with methadone and buprenorphine, which do not eliminate physical dependence on opioids. These medications instead reduce the use of illicit opioids and produce very strong positive health outcomes as measured by decreased mortality, improved mental and physical health, and reduced risk of disease transmission [93]. Considering the high rate of relapse after detoxification, maintenance therapy with methadone or buprenorphine is currently considered to be the first-line treatment for patients with opioid dependence [64]. Both agents are superior to withdrawal management alone and both significantly reduce illicit opioid use [94].

Any treatment for opioid dependence must take into consideration the chronic relapsing nature of opioid dependence, characterized by a variable course of relapse and remission in many patients. Treatments should emphasize patient motivation, psychoeducation, continuity of care, integration of

pharmacotherapy and psychosocial support, and improved liaison between the treatment staff and the judicial system. Pharmacotherapy must be offered in a comprehensive healthcare context that also addresses the psychosocial aspects of dependence [64]. Patients who are dependent on opioids frequently suffer from physical and psychiatric disorders, and targeted interventions of psychiatric comorbidity are essential in improving treatment outcome for these patients [64]. Polysubstance abuse is the rule rather than the exception in opioid dependence, and concurrent use of other substances should be carefully monitored and treated when necessary [64]. Concurrent use of other drugs or active engagement in other addictive behaviors should lead to consideration of other treatment plan components for the patient. The presence of co-occurring substance use disorders should provoke a re-evaluation of the level of care in which the patient is treated [94]. Incarceration should never automatically result in discontinuation of an existing treatment; imprisonment offers a window of opportunity to initiate or restart treatment with a necessary continuation after release [64].

Agonist Replacement Therapy

The goal of opioid replacement therapy is to reduce illicit drug use and associated health risks, with secondary goals of reducing unsafe sexual practices, improving vocational and psychosocial functioning, and enhancing quality of life [72]. The theoretical basis of opioid replacement stems from the finding that chronic opioid use results in an endogenous opioid deficiency as a result of the down-regulation of opioid production. This creates overwhelming cravings and necessitates interventions that shift the patient's attention and drive from obsessive preoccupation with the next use of opioids to more adaptive areas of focus, such as work, relationships, and non-drug leisure activities [72].

The neurobiologic changes resulting from prolonged opioid exposure provide a rationale for specific pharmacotherapies, such as long-acting opioid agonists, that are aimed at stabilizing these complex systems [95]. Opioid agonist maintenance treatment stabilizes brain neurochemistry by replacing short-acting opioids, which can create rapid changes in opioid levels in the serum and brain, with a long-acting opioid that has relative steady-state pharmacokinetics. Opioid agonist maintenance treatment is designed to have minimal euphoric effect, block the euphoria associated with administration of exogenous opioids (competitive antagonism), eliminate the risk of infectious disease and health consequences associated with injection drug use, and prevent opioid withdrawal [95].

Successful maintenance treatment entails stabilization of opioid dependence through opioid receptor occupation. Positron emission tomography studies have revealed that only 25% to 35% of brain opioid receptors are occupied during steady-state methadone maintenance, suggesting that unoccupied opioid receptors disrupted during cycles of opioid abuse could normalize during methadone maintenance [72]. Additionally, opioid replacement therapy blocks much of the euphoria from illicit heroin use. Long-term opioid agonist treatment also has a positive impact on public health, through significantly reducing overdose deaths, criminal activity, and the spread of infectious disease [72].

As of 2020, there were 1,754 treatment programs including opioid replacement therapy in the United States [96]. However, this represents less than 20% of all patients with opioid use disorder. Although some have criticized the practice of methadone and buprenorphine therapy on the grounds that one opioid is merely being substituted for another, the clinical benefits strongly support this treatment modality [72]. When compared to active street heroin users, these benefits include a four-times lower HIV seroprevalence rates, 70% fewer crime-days per year, and a one-year mortality rate of 1% (versus 8%) [97].

Abstinence-Oriented Therapies

The primary goal of abstinence-oriented interventions is cure, which is defined as long-term, stable abstinence from all opioids. Abstinence is achieved in two phases: detoxification and relapse prevention. Outcomes in abstinence-oriented programs are generally poor [64].

The primary goal of pharmacotherapy during detoxification is to alleviate opioid withdrawal severity and associated distress/medical complications and to enhance patient motivation to continue treatment. Withdrawal can also be reduced by psychosocial measures, such as contingency management or counseling, and as discussed, the addition of psychosocial therapy to pharmacologic treatment increases efficacy. Buprenorphine and clonidine are both used to manage withdrawal symptoms, but buprenorphine's advantages, compared with clonidine, are related to its favorable side effect profile and positive effects on well-being and psychosocial variables [64].

12-Step/Self-Help Programs

Twelve-step programs for opioid abuse and dependence include Narcotics Anonymous (NA), Heroin Anonymous (HA), and Methadone Anonymous (MA) and are modeled after Alcoholics Anonymous (AA), an abstinence-based support and self-improvement program that is based on the 12-step model of recovery. AA has helped hundreds of thousands of alcoholics achieve sobriety [98]. The 12-step model emphasizes acceptance of dependence as a chronic, progressive disease that can be arrested through abstinence but not cured. Additional elements include spiritual growth, personal responsibility, and helping other addicted persons. By inducing a shift in the consciousness of the addict, 12-step programs offer a holistic solution and are a resource for emotional support [98]. Although research on efficacy and patient outcomes in NA and MA is very limited, many prominent researchers emphasize the important role ongoing involvement in 12-step programs plays in recovery from substance abuse [99].

The understanding of drug dependence as a chronic and relapsing disorder has helped professionals gain a better comprehension of the vital role played by 12-step programs. Every patient attempting to recover from a substance use disorder will encounter a time when he or she faces urges to use without the resources or assistance of healthcare professionals. Twelve-step programs are not considered treatment, nor are they intended as substitutes for treatment. Instead, they are organizations that provide ongoing and indefinite support in the achievement and maintenance of abstinence and in personal growth and character development [99].

Part of the effectiveness of NA, HA, and MA is related to their ability to provide a competing and alternative reinforcer to drug use. Involvement in 12-step programs can enhance the quality of social support and the social network of the member, a potentially highly reinforcing aspect the person stands to forfeit if they resume drug using. Other reinforcing elements of 12-step involvement include recognition for increasingly durable periods of abstinence and frequent awareness of the consequences of drug and alcohol use through attendance of meetings [100]. Research shows that establishing a pattern of 12-step program attendance early in treatment predicts the level of ongoing involvement. Emphasis and facilitation of early engagement in a 12-step program involvement are key [101].

STIGMA OF ADDICTION

Many terms used in discussions of opioid use and misuse may have ambiguous meanings, and the absence of consensus in the terminology and definitions of substance use, substance use disorders, and addiction has led to considerable confusion and misconceptions. These misconceptions may be harbored by clinicians, patients, family members, and the public and can negatively impact patient interaction, assessment, treatment, and outcomes. This, coupled with pervasive stereotypes about what an opioid addict "looks" like, can negatively impact willingness to receive treatment or seek help and impair the patient's self-worth and mental health. Correction of these erroneous beliefs and attitudes is important, as is the use of nonpejorative and nonstigmatizing language when describing opioid analgesics, the patients who need them, and patients who develop aberrant behaviors or addiction involving opioids [31; 102]. It is important for all healthcare professionals to remember that addiction can affect any patients, regardless of age, sex, socioeconomic status, education, ability, or race.

PROGNOSIS OF TREATMENT FOR OPIOID USE DISORDER

The relapse rate among patients receiving treatment for opioid dependence and other substance abuse is high (25% to 97%), comparable to that of other patients with chronic relapsing conditions, including hypertension and asthma [103]. Many cases of relapse are attributable to treatment noncompliance and lack of lifestyle modification [104].

Duration of agonist replacement therapy is usually recommended as a minimum of one year, and some patients will receive agonist replacement therapy indefinitely. Longer durations of treatment are associated with higher rates of abstinence from illicit opioids [93].

Much remains unknown about patient outcomes following termination of long-term opioid replacement therapy. Some patients aim to achieve total abstinence from all opioids, but little is known about patient characteristics and strategies used among those who remain abstinent. It is likely that at least some of the patients who remain abstinent from all opioids do so with the help of a 12-step support program, such as NA [93].

CONCLUSION

Opioid analgesic medications can bring substantial relief to patients suffering from pain. However, the inappropriate use, abuse, and diversion of prescription drugs in America, particularly prescription opioids, has increased dramatically in recent years and has been identified as a national public health epidemic. A set of clinical tools, guidelines, and recommendations are now available for prescribers who treat patients with opioids. By implementing these tools, the clinician can effectively address issues related to the clinical management of opioid prescribing, opioid risk management, regulations surrounding the prescribing of opioids, and problematic opioid use by patients. In doing so, healthcare professionals are more likely to achieve a balance between the benefits and risks of opioid prescribing, optimize patient attainment of therapeutic goals, and avoid the risk to patient outcome, public health, and viability of their own practice imposed by deficits in knowledge.

Customer Information/Answer Sheet/Evaluation insert located between pages 60–61.

COURSE TEST - #95152 RESPONSIBLE AND EFFECTIVE OPIOID PRESCRIBING

This is an open book test. Please record your responses on the Answer Sheet.
A passing grade of at least 70% must be achieved in order to receive credit for this course.

In accordance with the AMA PRA Category 1 Credit™ system,
physicians must complete and pass a post-test to receive credit.

This 3 credit activity must be completed by April 30, 2027.

1. Inappropriate opioid analgesic prescribing for pain is defined as
- A) *non-prescribing.*
- B) *inadequate prescribing.*
- C) *continued prescribing despite evidence of ineffectiveness of opioids.*
- D) *All of the above*

2. When opioids are used for acute pain, clinicians should prescribe
- A) *the highest safe dose.*
- B) *extended-release opioids.*
- C) *a quantity no greater than that needed for the expected duration of severe pain.*
- D) *All of the above*

3. A patient prescribed opioids for chronic pain who is 65 years of age and displays high levels of pain acceptance and active coping strategies is considered at what level of risk for developing problematic opioid behavioral responses?
- A) *Low*
- B) *Medium*
- C) *High*
- D) *Severe*

4. The Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R)
- A) *consists of 5 items.*
- B) *is patient administered.*
- C) *diagnoses depression in the past month.*
- D) *assesses the likelihood of current substance abuse.*

5. Which of the following is NOT one of the 5 A's of monitoring chronic opioid response?
- A) *Analgesia*
- B) *Acceptance*
- C) *Affect (i.e., patient mood)*
- D) *Aberrant drug-related behaviors*

6. For patients considered at medium risk for misuse of prescription opioids, urine drug testing should be completed every
- A) *6 to 12 weeks.*
- B) *3 to 6 months.*
- C) *6 to 12 months.*
- D) *1 to 2 years.*

7. Which of the following statements regarding the disposal of opioids is TRUE?
- A) *Patients are almost always advised of what to do with unused or expired medications.*
- B) *There are no universal recommendations for the proper disposal of unused opioids.*
- C) *According to the FDA, most medications should be flushed down the toilet instead of thrown in the trash.*
- D) *All of the above*

8. The most common source of nonmedical use of prescribed opioids is from
- A) *a friend or relative for free.*
- B) *a prescription from one doctor.*
- C) *purchase from a drug dealer or other stranger.*
- D) *theft from a doctor's office, clinic, hospital, or pharmacy.*

9. Which of the following behaviors is the most suggestive of an emerging opioid use disorder?

A) Asking for specific medications
B) Injecting medications meant for oral use
C) Reluctance to decrease opioid dosing once stable
D) Stockpiling medications during times when pain is less severe

10. Which government agency is responsible for formulating federal standards for the handling of controlled substances?

A) Institutes of Medicine
B) U.S. Drug Enforcement Administration
C) Office of National Drug Control Policy
D) U.S. Department of Health and Human Services

Be sure to transfer your answers to the Answer Sheet insert located between pages 60–61.
PLEASE NOTE: Your postmark or facsimile date will be used as your test completion date.

Falls and Fall Prevention

Special Approvals

This course meets the California Requirement for geriatric medicine education.

This course meets 3 hours of risk management/professional responsibility education.

For more information regarding your CME requirements, please go to: www.NetCE.com/ce-requirements/physicians (for MDs and DOs) or www.NetCE.com/ce-requirements/physician-assistants (for PAs).

In addition to receiving *AMA PRA Category 1 Credit™*, physicians participating in Maintenance of Certification will receive the following points appropriate to their certifying board: 3 ABIM MOC Points, 3 ABS MOC Point.

Audience

This course is designed for physicians, physician assistants, nurses, 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.

A full Works Cited list is available online at www.NetCE.com.

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Division Planner
Ronald Runciman, MD

Senior Director of Development and Academic Affairs
Sarah Campbell

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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.

EPIDEMIOLOGY

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

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.

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].

TYPES 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].

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].

FALL RISKS

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

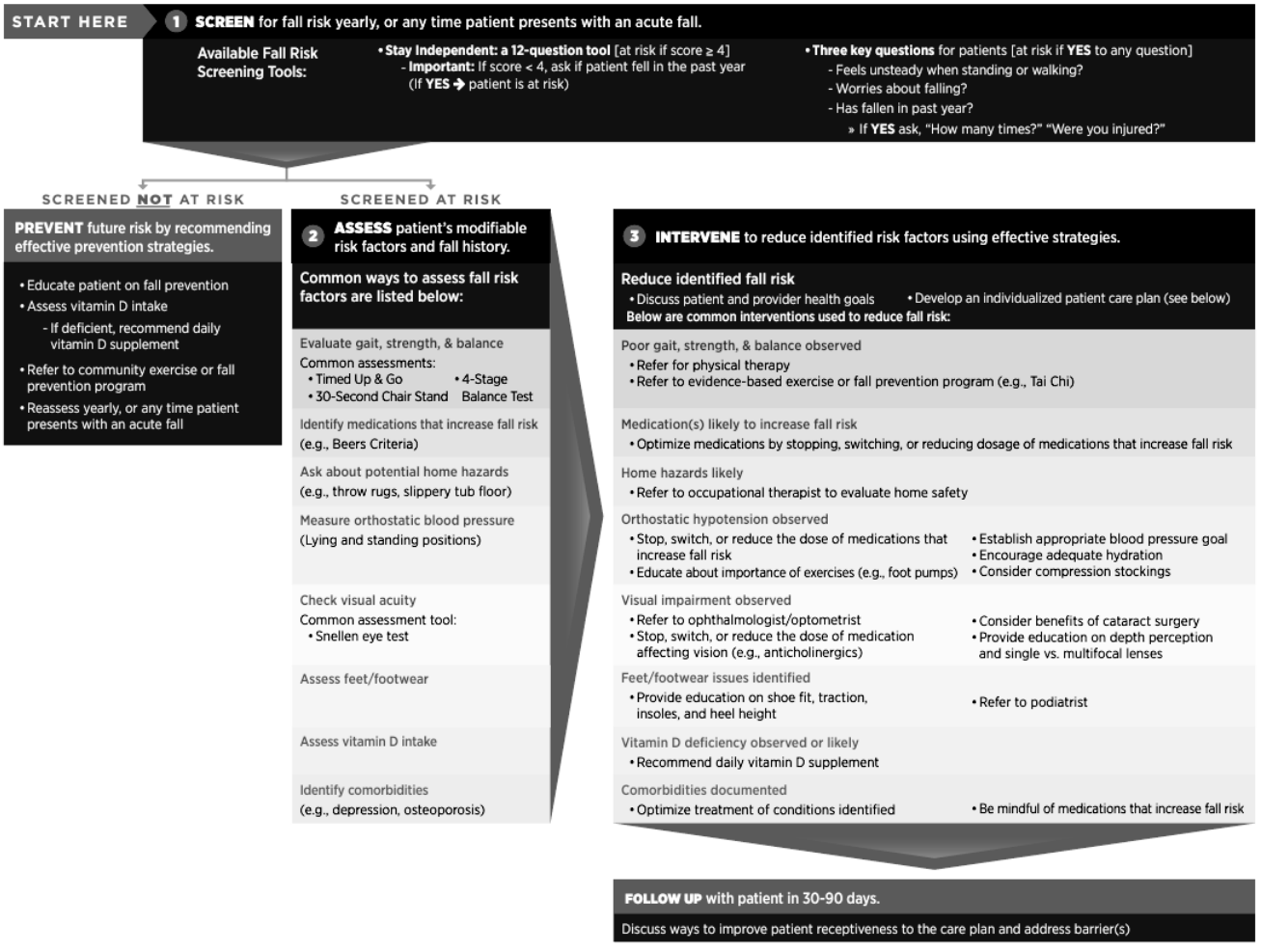
Exercise interventions are the cornerstone for fall risk reduction and prevention of fall-related injury in community-dwelling older adults. According to the U.S. Preventive Services Task Force (USPSTF), both supervised individual and group classes are effective when functional training is included [31]. 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.

INPATIENT AND RESIDENT FALL PREVENTION PRACTICES

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].

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



Source: [29] *Figure 1*

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)

SUGGESTED TASKS FOR SAFE MOBILITY AND FALL PREVENTION PROGRAM TEAM MEMBERS	
Team Member	**Suggested Tasks**
STEADI safe mobility champion (from any profession)	• Proactively encourage early mobilization of patients to reduce fall risks during hospitalization • Work with team to incorporate the safe mobility and fall prevention program into the patient care workflow • Work with available unit-based or hospital educators to establish a training program for current and future employees • Be available to troubleshoot issues during implementation • Provide feedback to team members • Monitor and report results of program implementation • Communicate with hospital leadership about the program • Assign and train staff to discuss fall prevention strategies with patients and caregivers
Nurse and/or certified nursing assistant	• Screen patients for fall risk using a screening tool (e.g., Stay Independent checklist, three key questions, STRATIFY Risk Assessment Tool) • Perform gait testing (e.g., Timed Up and Go Test, 30-Second Chair Stand Test, or 4-Stage Balance Test) • Check orthostatic blood pressure • Educate patients about orthostatic hypotension and related fall risk • Discuss fall prevention strategies with patients and caregivers • Perform vision assessment (e.g., Snellen eye chart) • Counsel about using single distance lenses when walking outside (e.g. avoid bifocals) • Assess feet and footwear • Conduct cognitive assessment (e.g., Mini-Cog) • Ensure each patient has optimal independence in instrumental activities of daily living (IADLs) and activities of daily living (ADLs) during hospital stay • Mobilize patient at least three times a day as tolerated • Give patient appropriate STEADI patient educational materials • Follow up during their hospital stay to ensure patients are making progress as part of fall prevention care plan
Physician, nurse practitioner, physician assistant, clinical nurse specialist	• Take a fall history, including circumstances of previous falls • During physical exam include an observation of gait to identify medical issues that could increase fall risk (e.g., cardiac or neurologic disease) • Review results of fall risk assessments performed by other team members • Avoid prescribing and manage medications that increase fall risk (collaborate with pharmacists) • Order appropriate labs and imaging specific to fall risk • Recommend and provide referrals specific to fall risk • Discuss fall prevention strategies with patients and caregivers • Engage patients and caregivers in developing and implementing individual fall prevention care plans • Avoid issuing bed rest orders or discontinue them as soon as not clinically indicated • Discontinue tethers (IV lines, urinary catheters, etc.) as soon as not clinically indicated • Recommend community exercise or fall prevention programs
Pharmacist	• Review medications to identify those that increase fall risk • 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 • Make recommendations for dose reduction or safer alternatives for medications that increase fall risk • Raise awareness about medication-related fall risks • Discuss fall prevention strategies with patients and caregivers

Table 1 continues on next page.

SUGGESTED TASKS FOR SAFE MOBILITY AND FALL PREVENTION PROGRAM TEAM MEMBERS *(Continued)*	
Team Member	**Suggested Tasks**
Physical therapist	• Assess or inquire about baseline functional status • Discuss fall prevention strategies with patients and caregivers • Perform detailed gait and balance testing • Design a rehabilitation care plan or exercise program to improve mobility and balance during hospitalization • Educate patients about community-based fall prevention programs, such as tai chi classes or Stepping On
Occupational therapist	• Discuss fall prevention strategies with patients and caregivers • Educate patients about home trip hazards (e.g. throw rugs, stairs) • Recommend fall prevention safety features (e.g., grab bars, lighting, railings) • Educate patients and caregivers about behavioral and functional changes that impact fall risk
Source: [22]	*Table 1*

- 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.

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/steadi/materials.html

Algorithm for Fall Risk Screening, Assessment, and Intervention

https://www.cdc.gov/steadi/pdf/STEADI-Algorithm-508.pdf

Timed Up and Go (TUG) Test

https://www.cdc.gov/steadi/pdf/STEADI-Assessment-TUG-508.pdf

4-Stage Balance Test

https://www.cdc.gov/steadi/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/Answer Sheet/Evaluation insert located between pages 60–61.

COURSE TEST - #91660 FALLS AND FALL PREVENTION

This is an open book test. Please record your responses on the Answer Sheet.
A passing grade of at least 70% must be achieved in order to receive credit for this course.

In accordance with the AMA PRA Category 1 Credit™ system,
physicians must complete and pass a post-test to receive credit.

This 3 credit activity must be completed by March 31, 2027.

1. How many falls severe enough to require medical attention occur worldwide each year?
- A) *18.4 million*
- B) *37.3 million*
- C) *58 million*
- D) *2 billion*

2. What are DALYs?
- A) *Daily amount life years*
- B) *Daily adjusted life years*
- C) *Disability-adjusted life years*
- D) *Daily adjusted limited yearsy*

3. Of falls that result in injury severe enough to require medical attention, what proportion require treatment for fracture?
- A) *5%*
- B) *20%*
- C) *50%*
- D) *95%*

4. Pediatric falls are the
- A) *1st leading cause of unintentional death in children.*
- B) *4th leading cause of unintentional death in children.*
- C) *7th leading cause of unintentional death in children.*
- D) *10th leading cause of unintentional death in children.*

5. What are the three main categories of falls?
- A) *Expected, sentinel, and caused*
- B) *Sentinel, non-sentinel, and fatal*
- C) *Preventable, inadvertent, and psychological expected*
- D) *Physiological anticipated, physiological unanticipated, and accidental*

6. According to the Joint Commission, a sentinel event is best characterized as a/an
- A) *challenging event.*
- B) *preventable event.*
- C) *warranted event causing injury or death.*
- D) *unexpected occurrence resulting in death or serious physical or psychological injury, or risk thereof.*

7. When did falls become part of the CMS "no-pay" policy?
- A) *1985*
- B) *1999*
- C) *2008*
- D) *2019*

8. Which of the following is an intrinsic fall risk factor?
- A) *Poor lighting*
- B) *Loose carpets*
- C) *Reduced visual acuity*
- D) *Lack of personal ambulation aids (if needed)*

9. For inpatients or residents, fall risk assessment and preventive interventions should start
- A) *at initial admission.*
- B) *when discharge planning.*
- C) *after the patient's first fall.*
- D) *only if the patient is determined to be at high risk.*

10. Which of the following tasks is the responsibility of the STEADI safe mobility champion?
- A) *Mobilize patient at least three times a day as tolerated*
- B) *Review medications to identify those that increase fall risk*
- C) *Avoid issuing bed rest orders or discontinue them as soon as not clinically indicated*
- D) *Work with team to incorporate the safe mobility and fall prevention program into the patient care workflow*

Be sure to transfer your answers to the Answer Sheet insert located between pages 60–61.
PLEASE NOTE: Your postmark or facsimile date will be used as your test completion date.

Chronic Cough in Adults

In addition to receiving *AMA PRA Category 1 Credit™*, physicians participating in Maintenance of Certification will receive the following points appropriate to their certifying board: 10 ABIM MOC Points, 10 ABA MOCA Points, 10 ABS MOC Points, 10 ABPath CC Points.

Audience
This course is designed for physicians, physician assistants/associates, and nurses 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
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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 activity has been approved for the American Board of Anesthesiology's® (ABA) requirements for Part II: Lifelong Learning and Self-Assessment of the American Board of Anesthesiology's (ABA) redesigned Maintenance of Certification in Anesthesiology Program® (MOCA®), known as MOCA 2.0®. Please consult the ABA website, www.theABA.org, for a list of all MOCA 2.0 requirements. Maintenance of Certification in Anesthesiology Program® and MOCA® are registered certification marks of the American Board of Anesthesiology®. MOCA 2.0® is a trademark of the American Board of Anesthesiology®.

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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, and 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

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 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, peripheral 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.

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

Source: [5; 9; 26] *Table 1*

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.

COUGH SEVERITY 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].

EPIDEMIOLOGY

PREVALENCE

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].

COUGH MEASURES		
Name	**Domains/Items, Rating and Minimal Clinically Importance Difference (MCID)**	**Comments**
Health-related quality of life patient-reported outcome tools		
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 ≥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.
Objective assessment tools		
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: ≥20% to 30% decrease	Does not capture the episodic nature of chronic cough, a primary factor in patients' disease burden
Subjective tools		
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*

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].

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 departments. 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: ≤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 ≤2.5 mcm in diameter (or PM2.5) 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].

PATIENT IMPACT OF CHRONIC COUGH

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

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 of 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].

NATURAL HISTORY AND DISEASE COURSE

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].

PATHOPHYSIOLOGY OF CHRONIC COUGH

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 intrathoracic 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-δand C fibers, sensory neurons originating from brainstem vagal ganglia that innervate the larynx and proximal airways. A-δ 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

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.

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.

"RED FLAG" ASSESSMENT OF SERIOUS UNDERLYING CAUSES OF COUGH

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]:

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[a]	X	X	X	X
[a]Diagnostic-Therapeutic Trials				
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*

- 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 recogniz-

ing 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].

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) 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 ≥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 INVESTIGATIONS IN PATIENTS WITH CHRONIC COUGH		
Investigation	**Description**	**Utility**
Lower Airway		
Chest radiograph	Plain radiograph of the chest from anterior or posterior aspect (occasionally lateral view)	**Mandatory**. 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)	**Mandatory** test for airflow obstruction. FEV1 ≤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 ≥12%, or ≥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 ≥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	**Mandatory** in all patients with suspected inhaled foreign body. Endobronchial appearance typically normal in chronic cough with normal chest x-ray.
Upper Airway		
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.
Other		
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*

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].

IDENTIFICATION AND MANAGEMENT OF UNDERLYING ETIOLOGIES

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 AACCP 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 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-γ (IFN-γ) and tumor necrosis factor-α (TNF-α), inducing bronchial epithelial apoptosis and remodeling. TNF-α promotes neutrophilic inflammation, which correlates with sputum TNF-α 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 nonsteroidal 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-γ 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-γ. Non-type 2 inflammation (i.e., neutrophils and IFN-γ) 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.

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 enhancement 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 heterogenous 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].

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*

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].

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].

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

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 H2-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

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*

- 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 H2-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 transdiagnostic 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].

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*

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 ≥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.

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].

GUIDELINE RECOMMENDATIONS FOR NEUROMODULATOR TREATMENT OF REFRACTORY/UNEXPLAINED CHRONIC COUGH						
Drug	**Guideline Organization (Year)**					
	ACCP (2016)	**ERS (2020)**	**GRS (2020)[a]**	**FRS (2023)**	**BTS (2023)**	**NEURO-COUGH (2023)**
Low-dose morphine slow-release	Not reported[b]	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

[a]"Can be used" is a weaker endorsement than "recommendation" (i.e., "should be used").
[b]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*

TREATMENT OF REFRACTORY 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].

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 α2δ 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].

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 ≥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 (≥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 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].

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/Answer Sheet/Evaluation insert located between pages 60–61.

COURSE TEST - #94820 CHRONIC COUGH IN ADULTS

This is an open book test. Please record your responses on the Answer Sheet.
A passing grade of at least 70% must be achieved in order to receive credit for this course.

In accordance with the AMA PRA Category 1 Credit™ system,
physicians must complete and pass a post-test to receive credit.

This 10 credit activity must be completed by July 31, 2027.

1. A cough lasting seven weeks is categorized as
- A) *acute.*
- B) *subacute.*
- C) *chronic.*
- D) *post-chronic.*

2. Cough hypersensitivity syndrome is
- A) *cough that persists despite guideline-based treatment of the presumed underlying cause(s).*
- B) *cough triggered by innocuous stimuli (e.g., laughing, talking, changes in ambient temperature).*
- C) *a distinct, often debilitating sensation of irritation or "itch" in the throat or chest that precede cough and is not satiated by coughing.*
- D) *a disorder characterized by cough triggered by mildly tussive or innocuous stimuli, with features of allotussia, hypertussia, and/or laryngeal paresthesia.*

3. Which of the following is an objective tool for cough measurement?
- A) *Visual Analog Scale (VAS)*
- B) *Cough Severity Diary (CSD)*
- C) *Leicester Cough Monitor (LCM)*
- D) *Cough Quality of Life Questionnaire (CQLQ)*

4. What is the approximate prevalence of chronic cough among U.S. adults?
- A) *1%*
- B) *10%*
- C) *25%*
- D) *50%*

5. Which of the following is a risk factor for the development of chronic cough?
- A) *Frailty*
- B) *Male sex*
- C) *Younger age*
- D) *Angiotensin-converting enzyme (ACE) inhibitor use*

6. Cough-induced rib fractures, a painful and potentially serious complication of chronic cough, often involve ribs
- A) *1 and 2.*
- B) *3 through 5.*
- C) *5 through 7.*
- D) *7 through 9.*

7. Studies of patients with chronic cough have reported high rates of
- A) *bipolar disorder.*
- B) *anxiety and depression.*
- C) *substance use disorders.*
- D) *ADHD and obsessive-compulsive disorder.*

8. Which of the following statements regarding the natural history and clinical course of chronic Cough is TRUE?
- A) *The natural history of cough hypersensitivity is clearly established.*
- B) *Most patients with chronic Cough are diagnosed and effectively treated within months.*
- C) *Chronic cough is related to an accelerated FEV1 decline over time, regardless of smoking history or COPD diagnosis.*
- D) *The relationship between chronic cough and worse clinical outcomes has a clear pathophysiological explanation.*

Test questions continue on next page →

9. What are the phases of cough?
- A) *Diastole and systole*
- B) *Waxing, full, and waning*
- C) *Inspiration, compression, and expiration*
- D) *Latent period, contraction, and relaxation*

10. Excessive coughing is a consequence of increased activation of neuronal cough-mediating pathways due to
- A) *Neuroplastic changes in the CNS*
- B) *Neuroplastic changes in vagal afferent fibers*
- C) *Excessive activation of airway vagal afferent terminals by chemical or mechanical irritants*
- D) *All of the above*

11. The first step in evaluating cough is to
- A) *identify its etiology.*
- B) *determine its duration.*
- C) *start empirical/diagnostic therapy.*
- D) *evaluate impact on patient quality of life.*

12. All of the following are "red flag" signs/symptoms in patients with chronic cough that warrant further evaluation, EXCEPT:
- A) *Hoarseness*
- B) *Hemoptysis*
- C) *History of asthma*
- D) *Systemic symptoms (e.g., fever, weight loss)*

13. In patients with negative physical examination and spirometry findings, what testing should be performed to confirm airway hyper-reactivity consistent with symptomatic asthma?
- A) *Laryngoscopy (fiberoptic)*
- B) *Chest computed tomography (CT)*
- C) *Peripheral blood eosinophil count*
- D) *Bronchial challenge testing (e.g., methacholine)*

14. Which of the following statements best describes the treatable traits approach in managing airway disease?
- A) *Traits in the treatable traits approach are defined as clinically relevant, measurable, and treatable.*
- B) *The treatable traits approach focuses solely on traditional diagnostic labels such as asthma and COPD to determine treatment plans.*
- C) *In the treatable traits approach, only phenotypes are considered for treatment, while endotypes are not relevant in identifying treatment targets.*
- D) *The treatable traits approach is limited to identifying and treating only those traits that are associated with conventional asthma and COPD diagnoses.*

15. In patients with chronic cough in asthma, the first-line treatment is
- A) *biologics.*
- B) *allergy medications.*
- C) *inhaled corticosteroid with or without long-acting beta-agonist*
- D) *a leukotriene receptor antagonist or long-acting muscarinic antagonist.*

16. Wheezing and NSAID hypersensitivity are features of which rhinitis phenotype?
- A) *Allergic*
- B) *GERD-associated*
- C) *Nonallergic noninfectious*
- D) *Chronic rhinosinusitis with or without nasal polyposis*

17. According to the 2016 ACCP clinical practice guideline for reflux-associated chronic cough, when should esophageal manometry and pH-metry be performed?
- A) *As a first-line diagnostic test for all patients with chronic cough, regardless of response to antireflux therapy.*
- B) *Only in patients who have not responded to a six-month antireflux trial, regardless of their surgical management plans.*
- C) *In patients who have responded partially to antireflux medication but do not have a clear diagnosis of gastroesophageal reflux.*
- D) *In patients with suspected reflux cough who are refractory to a three-month antireflux trial and are being considered for surgical management, or in those with strong clinical suspicion warranting diagnostic testing for gastroesophageal reflux.*

18. Which of the following agents is recommended by the American College of Chest Physicians for neuromodulator treatment of refractory/unexplained chronic cough?
- A) *Baclofen*
- B) *Gabapentin*
- C) *Amitriptyline*
- D) *Low-dose morphine slow-release*

19. In clinical trials, what is the most common side effect of nalbuphine extended-release?

A) Nausea
B) Fatigue
C) Dizziness
D) Constipation

20. Which of the following accurately describes the use of lidocaine in the context of treating chronic cough?

A) Lidocaine primarily functions as a systemic analgesic and is not effective for treating coughs associated with bronchoscopy or chronic cough.
B) Lidocaine selectively blocks specific types of sodium channels to reduce coughing during bronchoscopy, and it is not used for chronic cough.
C) Lidocaine's main role in treating chronic cough is through its action as a central nervous system depressant rather than its local anesthetic properties.
D) Lidocaine is a local anesthetic that non-selectively blocks voltage-gated sodium channels, which helps in reducing coughing during bronchoscopy and has been used in nebulized form to treat refractory chronic cough.

Be sure to transfer your answers to the Answer Sheet insert located between pages 60–61.
PLEASE NOTE: Your postmark or facsimile date will be used as your test completion date.

Depression and Suicide

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This course meets 4 hours of risk management/professional responsibility education.

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In addition to receiving *AMA PRA Category 1 Credit™*, physicians participating in Maintenance of Certification will receive the following points appropriate to their certifying board: 15 ABIM MOC Points, 15 ABS MOC Points, 15 ABA MOC Points, 15 ABP MOC Points, 15 ABPath Points.

Audience

This course is designed for physicians, nurses, physician assistants, social workers, therapists, and counselors in the primary care setting who may identify and treat patients who are depressed and/or suicidal.

Course Objective

Although contact with the primary care setting represents a potential opportunity for timely identification and intervention, abundant evidence indicates that many patients with depression are inadequately diagnosed and treated in these settings. The purpose of this course is to provide the information and encouragement necessary to allow primary care providers to properly diagnose, treat, and follow-up with patients with depression.

Learning Objectives

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

1. Outline the epidemiology of depression and suicide.
2. Identify populations at increased risk for depression.
3. Describe the natural history and pathophysiology of depression.
4. Evaluate the signs and symptoms of depression utilizing appropriate screening tools.
5. Employ the appropriate diagnostic criteria for depression, including modifier subtypes.
6. Assess patients for depressive signs and symptoms, with particular attention to unique features in special populations.
7. Identify other conditions that can mimic or co-occur with depression.
8. Create a treatment plan for patients diagnosed with depression.
9. Compare pharmacotherapies and psychosocial therapies used in the treatment of depression.
10. Assess patients' reactions to depression treatments and identify treatment-resistance depression.
11. Recognize and appropriately treat perinatal depression.
12. Review the epidemiology of suicide.
13. Describe the impact of suicide in the treatment of special populations, including among the elderly.
14. Identify risk and protective factors for suicide.
15. Evaluate tools available for the assessment and evaluation of suicide risk.

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.

A full Works Cited list is available online at www.NetCE.com.

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

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This activity has been approved for the American Board of Anesthesiology's® (ABA) requirements for Part II: Lifelong Learning and Self-Assessment of the American Board of Anesthesiology's (ABA) redesigned Maintenance of Certification in Anesthesiology Program® (MOCA®), known as MOCA 2.0®. Please consult the ABA website, www.theABA.org, for a list of all MOCA 2.0 requirements. Maintenance of Certification in Anesthesiology Program® and MOCA® are registered certification marks of the American Board of Anesthesiology®. MOCA 2.0® is a trademark of the American Board of Anesthesiology®.

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INTRODUCTION

Depression is a common, debilitating mood disorder that is highly prevalent in medically ill populations, but many persons with depression are unaware they need, or are reluctant to seek, professional help. Primary care contact represents a potential opportunity for timely identification and intervention, but many patients with depression are inadequately diagnosed by non-psychiatrist clinicians, even after additional training [1; 2]. Even with accurate diagnosis, treatment is often inconsistent with current evidence, reflecting poor provider competence and confidence related to diagnosing and treating depression [3]. Adverse outcomes may result from treatment non-adherence, which can be positively influenced by patient preference for the prescribed modality and shared decision-making between physician and patient [4; 5]. Shortcomings in the delivery of care by primary care physicians, nurses, and behavioral health professionals represent an opportunity to alleviate patient distress and improve functioning through education.

For some patients with major depressive disorder (MDD), their initial antidepressant is ineffective or intolerable, and others remain impaired despite substantial symptom reduction. Inadequate patient outcomes may result from limitations in the foundation of clinical care for depression: MDD is a highly heterogeneous disorder but is diagnosed as a unitary syndrome, and almost all U.S. Food and Drug Administration (FDA)-approved medications for depression are based on a 60-year-old mechanistic hypothesis. Knowledge advances are transforming the understanding and treatment of MDD. This course will discuss optimal use of standard diagnostic and therapeutic approaches, knowledge advances, and their consideration and integration into best practices of clinical care for patients with depression.

EPIDEMIOLOGY

INCIDENCE AND PREVALENCE OF DEPRESSION

In 2020, 18.4% of U.S. adults (one in five) reported having ever been diagnosed with depression. The prevalence of depression was higher in women, younger adults, and adults with lower education levels. Estimates of an ever diagnosis of depression ranged from 12.7% in Hawaii to 27.5% in West Virginia. Age-standardized county-level prevalence estimates ranged from 10.7% to 31.9%, with considerable state- and county-level variability [6]. Reports that focused on measures of current depression (i.e., during the prior two weeks) rather than on lifetime depression showed similar subgroup differences, including those observed both before and throughout the SARS-CoV-2 2019 (COVID-19) pandemic. Reporting from 2020 forward suggests that the COVID-19 pandemic contributed to a worsening mental health crisis in the United States, especially among adolescents and young adults [7; 8; 9].

Depression is more common in persons with medical illnesses, with 11% to 36% of general medical inpatients fulfilling diagnostic criteria for MDD [10; 11; 12; 13]. Depression also is two to three times more likely in individuals with chronic diseases, including diabetes, arthritis, and cardiovascular diseases [14].

According to data from the National Survey on Drug Use and Health (NSDUH), in 2021, an estimated 21 million Americans (8.3%) 18 years of age and older experienced a past-year major depressive episode, and 5 million (20.1%) American youth 12 to 17 years of age experienced a past-year major depressive episode [15].

DEMOGRAPHIC CHARACTERISTICS

NSDUH data indicate that women have higher rates of depression than men in every age group, with the highest rate occurring in individuals 26 to 49 years of age (11.1% in women; 7.5% in men) [15]. Rates of major depressive episodes among American Indian/Alaska Natives were 11.2%, compared with 8.4% among non-Hispanic White Americans [15]. Of the 21 million Americans 18 years of age and older who reported a past-year major depressive episode, approximately 15 million had episodes that included severe impairment. Of the 5 million young people 12 to 17 years of age who reported a past-year major depressive episode, approximately 3.6 million had episodes that included severe impairment. Female youth reported higher rates of severe impairment (22.1%) than male youths (7.8%) [15]. Social determinants of health (e.g., economic status, access to health care) also influence rates of depression [6]. Persons living below the poverty level are five times more likely to have current depression than those living at or above the poverty line [16].

Older Adults

The rate of depression in adults older than 65 years of age ranges from 1% to 5% in the community but increases to 13.5% in those who require home healthcare and to 11.5% in the hospitalized elderly [17]. The recurrence rate of MDD in the elderly is also extremely high, at 40% [18]. Chronic health conditions contribute to an increased risk of depression in the elderly [17].

Peripartum Women

The peripartum period may be the most common time in a woman's life for depression to develop. Between 14% and 23% of women will experience a depressive disorder while pregnant, and 10% to 15% of women will experience a depressive disorder postpartum [19; 20; 21].

Persistent Depressive Disorder

Persistent depressive disorder in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5-TR) represents a consolidation of DSM-IV-defined chronic MDD and dysthymic disorder. The 12-month prevalence in the United States is approximately 0.5% for persistent depressive disorder and 1.5% for chronic MDD [10]. The median age of onset of persistent depressive disorder is 31 years [22].

PERSONAL AND SOCIETAL COSTS OF DEPRESSION

Major depressive disorder exacts an enormous toll on afflicted persons and is recurrent or chronic in approximately 35% of patients. It is associated with numerous chronic medical comorbidities and complications from acute medical illness, such as myocardial infarction [22]. Interpersonal connections and role functioning as spouse, parent, or worker are impaired. MDD is the leading cause of disability in the United States for persons 15 to 44 years of age and is second only to chronic back and neck pain in disability days per year among all Americans [22].

MDD is among the most costly illnesses in the world. The cost of depression in the United States was estimated at $210.5 billion in 2010, a 21.5% increase from 2005 [23]. Approximately 50% of this figure was attributed to workplace costs, 45% to direct costs, and 5% to suicide-related costs [23; 24]. The economic burden of MDD was an estimated $236 billion in 2018, an increase of more than 35% since 2005 [25]. From 2010 to 2018, the largest increase was in workplace costs, which rose from 48% of depression-related costs in 2010 to 61% of costs in 2018. The direct cost of treating depression accounted for only 11.2% of the overall economic burden. For every dollar of direct costs, an additional $2.30 was spent on depression-related indirect costs [25]. Even low-grade depression is associated with decreased work productivity [26]. Patients who do not achieve full treatment response use twice as many healthcare services, and cost employers almost four times as much as patients achieving remission [27]. Women with early-onset depression (before 22 years of age) often fail to graduate from college and earn substantially less income than women with later-onset depression or no depression [28]. In the United States, the annual cost of suicidal behaviors (attempts and deaths) was estimated to be $93.5 billion in 2016 [29]. Depression causes an estimated 200 million lost workdays each year at a cost to employers of $17 to $44 billion [30]. However, attempts to quantify such costs on a national scale are hampered by incomplete data, such as the under-reporting of suicides [31].

BACKGROUND

RISK FACTORS

Several demographic/socioeconomic, psychosocial, familial, medical, and psychologic factors are associated with higher risk for depression. Adverse early life events such as early childhood parental abandonment or death, or emotional trauma from physical, sexual or emotional abuse are major risk factors for depression and other psychiatric disorders in adulthood. In adulthood, recent loss (e.g., death, divorce), domestic abuse/violence, traumatic civilian (assault, serious car accident) or military (battlefield injury, witnessing death and dismemberment) events, and major life changes (e.g., job change, financial hardships) are all potential red flags for depression [21; 32].

Women have greater risk of depression, with a lifetime prevalence almost twice that of men [33]. Among women, severe obesity (body mass index greater than 40) is strongly associated with depression [34]. Lower socioeconomic status and being single are also risk factors for both genders [32].

Family history of psychopathology, affective disorders in general, and major depression are particularly robust risk factors. MDD is two to four times more common among persons with an afflicted first-degree biologic relative (a parent or sibling) than among the general population [10]. Relative risks appear to be higher for early-onset and recurrent forms [10]. However, family studies indicate that major depression is not caused by any single gene but is a disease with complex genetic features. No specific genetic risk factor has been reliably identified and associated with the development of depression [35].

Certain neurologic disorders are risk factors, such as Parkinson disease, stroke, multiple sclerosis, and seizure disorders. Among persons with certain general medical conditions, such as cancer, diabetes, myocardial infarction, or stroke, 20% to 25% will go on to experience a major depressive episode (MDE) [22]. Chronic pain, medical illness, and persistent or severe psychosocial stress elevate the risk of MDD [32].

Risk factors for late-onset depression include widowhood, physical illness, educational attainment less than high school, impaired functional status, and heavy alcohol consumption [21; 36].

As noted, peripartum women are particularly vulnerable to depression. Risk factors for peripartum depression include [21]:

- Depression or anxiety during pregnancy
- Previous history of a mood disorder
- Poor social support
- Stressful life events
- Pre-pregnancy and gestational diabetes
- Fragmented or poor sleep
- Substance abuse
- Current or past abuse experiences
- Difficulty breastfeeding in the first two months postpartum

NATURAL HISTORY OF DEPRESSION

Onset of a first major depressive episode (MDE) can be triggered by a serious psychosocial stressor and is associated with a history of panic attacks and alcohol or substance use disorder [21; 37]. A prodromal syndrome of anxiety or low-grade depression symptoms may persist for several months before onset of an initial MDE. Major depression has a variable age of onset, but the mid- to late-20s is typical [10; 22].

After the initial onset of MDD, around 15% of patients have a chronic and unremitting course. An additional 35% recover but experience one or more future recurrent episodes, and roughly 50% of first lifetime onsets recover and do not have future MDE episodes [10; 37]. The risk of recurrence becomes progressively lower over time as the duration of remission increases. Preceding severe depressive episodes, younger age, and previous multiple depressive episodes increase the risk of recurrence [10].

Antidepressant medication can alter the disease course by reducing relapse rates, while premature antidepressant discontinuation is associated with marked increases in risk of relapse [38; 39; 40]. Relapse prevention is a clinical priority, and a collaborative care model with ongoing pharmacotherapy and/or psychotherapy and regular follow-up can improve treatment adherence and reduce the risk of depressive relapse [21; 41]. A single episode of major depression is associated with a 50% chance of a subsequent episode, two episodes with a 70% chance, and three or more episodes with a 90% chance [42]. A greater number of depressive episodes predicts poor treatment response [22].

Depression is an illness with a potentially fatal outcome. Among persons with a mood disorder, 12% to 20% will ultimately die by suicide. The first three months is the period of highest risk for a first attempt, with the three months following the first attempt being the highest risk period for a second attempt [43].

DEFINITIONS

Several similar but distinct terms are used to describe depression. The DSM-5-TR states the common feature of depressive disorders is the "presence of a sad, empty, or irritable mood, accompanied by somatic and cognitive changes that significantly affect a person's ability to function" [10]. Depressive disorder is an umbrella term that includes MDD (including major depressive episode), persistent depressive disorder, premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder. A new diagnosis, disruptive mood dysregulation disorder (a chronic, severe, persistent irritability), is included in the DSM-5-TR to address concerns of potential overdiagnosis and treatment of bipolar disorder in children 12 years of age and younger [10]. MDD, formerly called major depression or clinical depression, is the classic condition in this group of disorders, characterized by discrete episodes of at least two weeks' duration involving clear-cut changes in affect, cognition, and functioning, with inter-episode remissions [10]. Persistent depressive disorder is a chronic, lower-grade depression that does not have the level of severity of MDD. A depressed mood (i.e., feeling sad) that occurs for most of the day, for more days than not, and for at least two years (or at least one year for children and adolescents) is the essential feature of this disorder [10].

PATHOPHYSIOLOGY OF DEPRESSION AND SUICIDE

PATHOPHYSIOLOGY OF DEPRESSION

The understanding of MDD pathophysiology and treatment is substantially changing. Until recently, the explanatory model of depressive illness and antidepressant drug efficacy was the monoamine hypothesis. Modern antidepressants were introduced in the 1950s following serendipitous discovery of anti-depressant effects with tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). Selective serotonin reuptake inhibitors (SSRIs) were introduced in the late 1980s, followed by atypical antidepressants and serotonin-noradrenaline reuptake inhibitors (SNRIs) [44]. The monoamine hypothesis, proposed to explain the unexpected effects of TCAs/MAOIs in the 1950s, posits that depression results from deficient brain serotonin (5-HT) and/or norepinephrine levels. This remained the dominant paradigm of depression and the basis of nearly all FDA-approved antidepressants for the next five decades [45; 46]. Limitations of the monoamine hypothesis and mechanistic homogeneity of standard antidepressants are now understood. MDD is vastly more complex and diverse than previously assumed, and novel pathways that underlie its pathophysiology have been identified [47; 48].

Inflammatory Pathways

"Inflammation" broadly describes immune-related processes within the body, a protective immunovascular response involving immune cells, blood vessels, and molecular mediators. Inflammatory response is activated by external (microbial infection) or internal (atherosclerosis) causes to maintain homeostasis, by eliminating initial cause of injury, clearing dead and damaged cells, and initiating tissue repair. A normal immune system produces pro- and anti-inflammatory mediators. When anti-inflammatory mediators cannot inhibit the pro-inflammatory immune response, a chronic inflammatory state may develop. Acute inflammation is adaptive (for clearing infection), but chronic inflammation is usually maladaptive and destructive and may persist for years as a low-grade state without clinical symptoms [49].

An inflammatory response produces prostaglandins, white blood cells, and cytokines that generate other inflammatory molecules, including tumor necrosis factor-alpha, interleukins, and C-reactive protein. These mediators communicate with other immune system elements. Central nervous system (CNS) inflammation (neuroinflammation) involves diverse cell types, microglia, and astrocytes that both induce and limit brain inflammatory processes [49]. Peripheral and central immune systems communicate through bidirectional pathways [50]. Inflammation is a core component of chronic mood disorders.

Early-Life Adversity

Early-life adversity (ELA) describes childhood trauma, abuse, or caregiver abandonment, and research demonstrably links ELA with inflammation and later depression. The brain and immune system are incompletely formed at birth; maturation is shaped by interaction with the postnatal environment. ELA can affect immune development, which can adversely affect development of brain regions involved in mood, cognition, and behavior [50]. ELA can also promote neuroendocrine, physiologic, behavioral, and psychologic changes that impair normal development of brain systems involved in learning, motivation, and stress response. A chronically over-reactive stress response system can impair stress response, emotional regulation, and impulse control in adulthood—a biologic priming for later depression [51; 52; 53; 54; 55]. The neurobiologic correlates of ELA and inflammation are striking, and impact on adverse clinical outcomes is demonstrated across psychiatric disorders [56].

Depression as Systemic Illness

More than 80% of patients with depression have medical comorbidity, and depression is viewed as a systemic illness [57]. Chronic inflammatory states and hyper-reactive immune response to stress in patients with MDD and ELA likely contribute to the high prevalence of inflammatory medical disorders in this population. The relationship between inflammation, inflammatory disorders, and depression is bidirectional; as these medical disorders persist, the chronic inflammatory state promotes the onset of depression [58; 59].

Patient-Treatment Matching

The limitations of standard pharmacotherapy for MDD have prompted efforts to identify patient subtypes for effective treatment matching. In a 2017 study, functional magnetic resonance imaging (fMRI) brain scans of 1,200 patients with MDD were analyzed and four unique biotypes (subtypes), distinct by patterns of abnormal functional connectivity in limbic and frontostriatal networks, were identified. For example, patients with biotype 1 showed severely impaired connectivity in brain regions that regulate fear-related behaviors and reappraisal of negative emotional stimuli. Treatment response to repetitive transcranial magnetic stimulation differed by subtype and was predicted with very high accuracy [60].

ASSESSMENT AND DIAGNOSIS OF DEPRESSION

As noted, depression is a disorder of mood involving disturbances in emotional, cognitive, and behavioral regulation. The mood disorder is considered secondary if it occurs in association with substance abuse or withdrawal and/or certain medications. The mood disorder is called primary if it does not occur in association with these conditions. Primary mood disorders are categorized into depressive (unipolar) and manic depressive (bipolar) conditions. Unipolar mood conditions are divided into MDD and persistent depressive disorder [21].

Biologic measures of depression are not available for clinical practice, and diagnosis is made through psychometric findings, fulfillment of diagnostic criteria, patient history, and clinical impression [61].

SIGNS AND SYMPTOMS OF DEPRESSION

Depression is often difficult to diagnose because patient presentation is diverse, and a mood disorder may not be obvious. Patients with MDD may not seek help for mood problems, but their presentation can reflect current depression. Presentations associated with depression in patients not complaining of depressed mood or anhedonia include [10; 62]:

Clinical Factors

- Previous personal or family history of depression
- Psychosocial adversity (divorce, domestic violence)
- High healthcare system utilizers
- Chronic medical conditions (especially cardiovascular disease, diabetes, neurologic disorders)
- Other psychiatric conditions
- Times of hormonal challenge (e.g., peripartum)

Symptom Factors

- Unexplained physical symptoms
- Chronic pain
- Fatigue
- Anxiety
- Substance abuse
- Weight gain or loss
- Sleep disturbance
- Dampened affect
- Complaints about memory, concentrating, making decisions

Assessment of the presence of depression can also be made through signs and symptoms of the following cognitive, affective, and behavioral domains [10; 21; 22].

Appearance and Affect

Although most patients with MDD appear normal upon initial presentation, patients with severe symptoms can exhibit poor grooming and hygiene and changes in weight from previous contact. Psychomotor retardation may be present, reflected by a slowing or absence of spontaneous movement, flat affect, and sighs and long pauses. This represents a diminished reactivity in emotional expression. Some patients with MDD may display psychomotor agitation, reflected by pacing, hand wringing, or hair pulling [10; 21; 22].

Mood and Thought Process

Patients may appear tearful or sad and often report a dysphoric mood state expressed as sadness, heaviness, numbness, or irritability and mood swings, as well as a loss of interest or pleasure in their recreational or leisure activities, difficulty concentrating, or loss of energy and motivation. Feelings of worthlessness, hopelessness, helplessness, or other negative thoughts may pervade their thinking, and ruminative thinking is not uncommon in MDD. Eye contact may be absent [10].

In the context of MDD, psychotic thought processes are congruent in content with the patient's mood state, examples being delusions of worthlessness or progressive physical decline. Evidence of psychotic symptoms requires careful assessment to rule out other contributing conditions such as bipolar disorder, schizophrenia or schizoaffective disorder, substance abuse, or organic brain syndrome [10; 22].

Cognition and Sensorium

Poor memory or concentration is a frequent complaint of patients with MDD, but actual cognitive deficits are infrequent and when present may represent pseudodementia. A fluctuating or depressed sensorium suggests delirium, and the patient should be evaluated for organic contributors [21; 22].

Speech

Speech in patients with MDD may be normal, slow, monotonic, or lacking in spontaneity and content. Pressured speech and racing thoughts are suggestive of mania, and disorganized speech may reflect psychosis [10; 21; 22].

Thought Content, Suicidality, and Homicidality

The thought content of patients with depression is usually consistent with the dysphoric mood and should always be assessed for hopelessness, suicidal ideation, or homicidal/violent ideation or intent. Previous suicide attempts or violence predicts future behavior, and command hallucinations are associated with increased suicidal and homicidal actions [21].

SCREENING

As of 2023, the U.S. Preventive Services Task Force recommends depression screening in the adult population, including pregnant and postpartum women and older adults (i.e., 65 years of age or older). Screening should be implemented with adequate systems in place to ensure accurate diagnosis, effective treatment, and appropriate follow-up [63].

The recommendation applies to adults 19 years of age or older who do not have a diagnosed mental health disorder or recognizable signs or symptoms of depression or suicide risk. The recommendation focuses on screening for MDD and does not address screening for other depressive disorders (e.g., minor depression, dysthymia) [63].

Depression screening instruments are used to identify patients who should undergo a fuller assessment for depressive disorders [64]. The Patient Health Questionnaire-2 (PHQ-2) is a two-question screen widely recommended for use in primary care [65]:

- "In the past two weeks, have you been bothered by little interest or pleasure in doing things?"
- "In the past two weeks, have you been feeling down, depressed, or hopeless?"

An answer of "yes" to either question requires a more detailed assessment.

The Patient Health Questionnaire-9 (PHQ-9) is the most-recommended instrument following a positive screen. It consists of nine questions that ascertain depressive symptoms and symptom severity in the past two weeks and takes two minutes to complete. The PHQ-9 is recommended for use to measure severity before treatment and for periodic use during therapy to help assess response [64; 66]. Positive response to the last item ("Thoughts that you would be better off dead or of hurting yourself in some way?") is associated with increased risk for suicide attempt [67].

Other screening and assessment tools are more complex, and others have extensive use in research. Some may be useful in assessing comorbid conditions or in differential diagnosis. They include [21; 64; 68; 69; 70]:

- Zung Self-Rating Depression Scale: A widely used depression measure.
- Beck Depression Inventory II (BDI-II): Widely used as a depression outcome measure in research and practice.
- Geriatric Depression Scale (GDS): Developed to assess depression in older adults.
- Hamilton Rating Scale for Depression (HAM-D or HDRS): Extensively used in clinical research.
- Montgomery-Åsberg Depression Rating Scale (MADRS): Greater sensitivity to medication or other treatment response than the HAM-D.
- Edinburgh Postnatal Depression Scale (EPDS): The most widely used assessment tool for postpartum depression, administered to patients six weeks after delivery.
- CAGE Questionnaire: Recommended due to high rates of excessive alcohol and substance use in depression. Use to screen patients undergoing further evaluation.
  Ask the patient if they have ever:
  - Felt you ought to cut down on your drinking (or drug use)?
  - Had people annoy you by criticizing your drinking (or drug use)?

  - Felt bad or guilty about your drinking (or drug use)?
  - Had a drink (or drug use) as an eye opener first thing in the morning to steady your nerves or get rid of a hangover or to get the day started?

Each affirmative response earns one point. One point indicates a possible problem. Two points indicate a probable problem.

- The Distress Thermometer: Developed for patients with significant language or communication difficulties, this one-question screen identifies distress from any source. The person marks a scale that asks: "How distressed have you been during the past week on a scale of 0 to 10?" Scores of 4 or more indicate significant distress that requires further investigation.

ASSESSMENT

As noted, a positive screen may indicate the presence and severity of depression, but it does not provide the clinical information required for diagnosis and treatment. Additional psychologic testing with the Millon Clinical Multiaxial Inventory-III (MCMI-III) or Minnesota Multiphasic Personality Inventory-2 (MMPI-2) can help determine diagnosis or differential diagnoses [71]. Both instruments should only be interpreted by licensed psychiatrists or psychologists with training in psychologic testing and assessment. Assessing for self-harm is also important. Persons who survive a serious suicide attempt may sustain injuries such as broken bones, brain damage, or organ failure and often experience continued depression and other mental health problems [72; 73].

An appropriate patient history includes information about the present illness, the medical history and medication history, including any substance abuse or dependence [21]:

- History of present illness: Determine onset, severity, prior history, concurrent psychiatric conditions, and psychosocial stressors
- Medical history: Rule out medical disorder cause of major depression
- Medication history and substance use disorder

DIAGNOSIS OF DEPRESSION

In 2013, the American Psychiatric Association (APA) published their most recently revised diagnostic criteria for depression and other psychiatric illness in the DSM-5, including major depression (i.e., MDD) [10]. The DSM-5 underwent a text revision in 2022, with the addition of prolonged grief disorder and new symptom codes that allow clinicians to indicate the presence or history of suicidal behavior and nonsuicidal self-injury.

As stated, the DSM-5-TR umbrella of depressive disorders includes MDD (including major depressive episode), persistent depressive disorder, premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, unspecified depressive disorder, and disruptive mood dysregulation disorder, a new diagnosis added to address concerns about the potential overdiagnosis of and treatment for bipolar disorder in children up to 12 years of age [10].

Persistent Depressive Disorder

Persistent depressive disorder is a depression of less severity than MDD that usually begins in childhood and adolescence. The depressed mood lasts for most of the day, for more days than not, must be present for at least two consecutive years (at least one year in children and adolescents), and must include the presence (while depressed) of two or more of the following symptoms [10]:

- Poor appetite or overeating
- Insomnia or hypersomnia
- Low energy or fatigue
- Low self-esteem
- Poor concentration or difficulty making decisions
- Feelings of hopelessness

Major Depressive Disorder

To meet the diagnosis of MDD, a person must have at least five of the following symptoms for at least two weeks' duration and represent a change from previous functioning. At least one of the symptoms must be either depressed mood or loss of interest or pleasure [10]:

- Depressed mood most of the day, nearly every day
- Markedly diminished interest or pleasure in all or almost all activities most of the day or nearly every day
- Significant weight loss or gain (>5% body weight) or increase or decrease in appetite
- Insomnia/hypersomnia nearly every day
- Psychomotor agitation or retardation nearly every day
- Fatigue/loss of energy nearly every day
- Feelings of worthlessness or inappropriate guilt nearly every day
- Diminished concentration or indecisiveness nearly every day
- Recurrent thoughts of death or suicide, suicide attempt, or a specific plan for attempting suicide

In addition, the symptoms must not meet the criteria for a mixed episode. The patient with MDD has never experienced a manic, mixed, or hypomanic episode. Symptoms should cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. Additionally, the symptoms may not be due to the direct physiologic effects of a recreational or prescribed drug or be better accounted for by bereavement (i.e., after the loss of a loved one, the symp-

toms persist for longer than two months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation) [10].

The diagnostic symptoms of MDD represent the domains of affective, behavioral, cognitive, and somatic impairment. Affective or mood symptoms include depressed mood and feelings of worthlessness or guilt, while behavioral symptoms include social withdrawal and agitation. Cognitive symptoms include difficulties with concentration or decision making, and somatic or physical symptoms include insomnia or fatigue.

The DSM-5-TR diagnostic criteria for MDD also include several specifiers to further describe the nature of the current episode of MDD. These specifiers include [10]:

- Anxious distress
- Mixed features
- Melancholic features
- Atypical features
- Mood-congruent psychotic features
- Mood-incongruent psychotic features
- Catatonic features
- Peripartum onset
- Seasonal pattern

Criteria for Anxious Distress Specifier

In order for a patient with MDD to be classified as meeting the criteria for anxious distress, he or she must have at least two of the following symptoms during the majority of days [10]:

- Feeling keyed-up or tense
- Feeling unusually restless
- Having difficulty concentrating due to worry
- Fearing that something awful may happen
- Worrying about losing control

High levels of anxiety are associated with higher suicide risk, longer duration of illness, and greater likelihood of treatment nonresponse. It is therefore clinically useful to accurately specify the severity level of anxious distress:

- Mild: Two symptoms
- Moderate: Three symptoms
- Moderate-to-severe: Four or five symptoms
- Severe: Four or five symptoms, with motor agitation

Criteria for Mixed Features Specifier

MDD with mixed features is a significant risk factor for the development of bipolar I or II disorder. A patient with MDD may be classified as meeting the criteria for mixed features when at least three of the following manic/hypomanic symptoms are present during the majority of days of a depressive episode [10]:

- Elevated, expansive mood
- Inflated self-esteem, grandiosity
- More talkative than usual or feeling pressure to continue talking
- Ideas, thoughts are racing
- Increase in energy or goal-directed activity
- Increased or excessive involvement in activities with high potential for painful consequences
- Decreased need for sleep

Criteria for Melancholic Features Specifier

For a patient with MDD to be classified as meeting the DSM-5-TR criteria for melancholic features he or she must have either a loss of pleasure in all, or almost all, activities or a lack of reactivity to usually pleasurable stimuli (i.e., does not feel much better, even temporarily, when something good happens). In addition, three (or more) of the following symptoms must be present [10]:

- Distinct quality of depressed mood (e.g., the depressed mood is experienced as distinctly different from the kind of feeling experienced after the death of a loved one)
- Depression regularly worse in the morning
- Early morning awakening (at least two hours before usual time of awakening)
- Marked psychomotor retardation or agitation
- Significant anorexia or weight loss
- Excessive or inappropriate guilt

Criteria for Atypical Features Specifier

Mood reactivity (i.e., mood brightens in response to actual or potential positive events) is the characteristic feature of MDD with atypical features. In addition, at least two of the following symptoms must be present [10]:

- Significant weight gain or increase in appetite
- Hypersomnia
- Leaden paralysis (i.e., heavy, leaden feelings in arms or legs)
- Long-standing pattern of interpersonal rejection sensitivity (not limited to episodes of mood disturbance) that results in significant social or occupational impairment

Essentially, atypical MDD is characterized by vegetative symptoms of reversed polarity (e.g., increased rather than decreased sleep, appetite, weight), marked mood reactivity, hypersensitivity to rejection, phobic symptoms, or a sense of severe fatigue that creates a sensation of leaden paralysis or extreme heaviness of the extremities [22].

Criteria for Mood-Congruent Psychotic Specifier

According to the DSM-5-TR, MDD with psychotic features includes the presence of delusions and/or hallucinations. Specifically, with mood-congruent psychotic features, the content of all delusions/hallucinations is consistent with the typical depressive themes (i.e., personal inadequacy, guilt, disease, death, nihilism, deserved punishment) [10].

Criteria for Mood-Incongruent Psychotic Specifier

The criteria for MDD with mood-incongruent psychotic features is satisfied when the content of delusions/hallucinations does not involve typical depressive themes or the content is a mix of mood-incongruent and mood-congruent themes [10].

Criteria for Catatonia Specifier

The specifier for catatonia can apply to an episode of depression if catatonic features are present during most of the episode. The clinical picture of the catatonic type of MDD is dominated by at least three of the following [10]:

- Stupor (i.e., motoric immobility; not actively relating to environment)
- Catalepsy (i.e., passive induction of a posture held against gravity)
- Waxy flexibility (i.e., slight, even resistance to positioning by examiner)
- Mutism (i.e., no, or very little, verbal response)
- Negativism (i.e., opposition or no response to instructions or external stimuli)
- Posturing (i.e., spontaneous and active maintenance of a posture against gravity)
- Mannerism (i.e., odd, circumstantial caricature of normal actions)
- Stereotypy (i.e., repetitive, abnormally frequent, non-goal-directed movements)
- Agitation, not influenced by external stimuli
- Grimacing
- Echolalia (i.e., mimicking another's speech)
- Echopraxia (i.e., mimicking another's movements)

Criteria for Peripartum Onset Specifier

Mood episodes can have their onset either during pregnancy or postpartum. Between 3% and 6% of women will experience the onset of a major depressive episode during pregnancy or in the weeks or months following delivery. Fifty percent of "postpartum" major depressive episodes actually begin prior to delivery [10]. Thus, these episodes are referred to collectively as peripartum episodes. Peripartum-onset mood episodes can present either with or without psychotic features. Postpartum mood (major depressive or manic) episodes with psychotic features appear to occur in from 1 in 500 to 1 in 1,000 deliveries. After a woman has had a postpartum episode with psychotic features, the risk of recurrence with each subsequent delivery is between 30% and 50%. This specifier may be applied to a current episode of MDD if the onset is within four weeks postpartum [10].

Criteria for Seasonal Pattern Specifier

According to the DSM-5-TR, MDD with seasonal pattern specifier can be applied to the pattern of major depressive episodes in MDD, recurrent. The essential feature is the onset and remission of major depressive episodes at characteristic times of the year. Criteria include [10]:

- A regular temporal relationship between the onset of MDD and a particular time of the year (e.g., fall, winter)
- Full remissions (or a change from MDD to mania or hypomania) at a characteristic time of the year (e.g., depression disappears in the spring)
- In the last two years, two MDD episodes have occurred that demonstrate the temporal seasonal relationships defined above and no nonseasonal major depressive episodes have occurred during that same period.
- Seasonal MDD episodes substantially outnumber the nonseasonal MDD episodes that may have occurred over the individual's lifetime.

Bereavement and Prolonged Grief Disorder

With bereavement, the loss of a loved one is a particularly severe stressor. Bereavement is commonly accompanied by the signs and symptoms of MDD, with roughly 25% of bereaved persons exhibiting a diagnosable major depression at two months and seven months following the loss [74]. The death of a loved one is followed by an intensely emotional and disruptive period that gradually attenuates as the death is comprehended and accepted and its consequences understood (integration). It is a highly stressful period accompanied by the need to attend to a range of things not usually on one's agenda. Most people meet the coping demands and are able to find a pathway through the sorrow, numbness, and even guilt and anger that are part of the normal grieving process. A small minority, however, do not cope effectively. For them, the feelings of loss become debilitating. They do not improve with the passing of time and can become so long-lasting and severe that recovering from the loss and resuming a normal life is impossible without assistance [75]. These people are suffering from prolonged grief disorder, a syndrome in which healing is impeded and acute grief is intense and prolonged. Individuals with more severe and prolonged major depressive manifestations tend to be younger with a history of previous episodes of major depression, and antidepressant medications or psychotherapy should be used in cases with prolonged depressive reaction with significant functional impairment [10; 22].

Prolonged grief disorder is the newest disorder to be added to the DSM. The disorder was added to the DSM-5-TR in 2022 after several decades of studies that suggested many people were experiencing persistent difficulties associated with bereavement that exceeded expected social, cultural, or religious expectations [10]. Prolonged grief disorder often co-occurs with other mental disorders (e.g., PTSD, anxiety, depression). Sleep problems, such as poor long-term sleep, occur in an estimated 80% of people with this disorder [501].

Prolonged grief disorder is defined as "intense yearning or longing for the deceased (often with intense sorrow and emotional pain) and preoccupation with thoughts or memories of the deceased. In children and adolescents, this preoccupation may focus on the circumstances of the death" [10]. In adults, this intense grief must still be present one year after a loss to be considered prolonged grief disorder; in children, the timeframe is six months. Additionally, the individual with prolonged grief disorder may experience significant distress or problems performing daily activities at home, work, or other important areas [10]. It is important for clinicians to differentiate prolonged grief disorder from usual acute grief, as well as depression and anxiety disorders [75]. Risk factors for prolonged grief disorder include past losses, separations that can impact current losses, and a history of depressive illness [115x]. Symptoms include [10]:

- Identity disruption (e.g., feeling as though part of oneself has died)
- A marked sense of disbelief about the death
- Avoidance of reminders that the person is dead
- Intense emotional pain (e.g., anger, bitterness, sorrow)
- Difficulty reintegrating (e.g., unable to engage with friends, pursue interests, plan for the future)
- Emotional numbness
- Feeling that life is meaningless
- Intense loneliness and feeling of being detached from others

An estimated 7% to 10% of bereaved adults will experience the persistent symptoms of prolonged grief disorder, and 5% to 10% of bereaved children and adolescents will experience depression, PTSD, and/or prolonged grief disorder [501; 502]. Treatments using elements of CBT have been found to be effective in reducing symptoms [10]. Complicated grief treatment incorporates components of CBT and other approaches to help patients adapt to the loss. It focuses on accepting the reality of the loss and on working toward goals and a sense of satisfaction in a world without the loved one [501]. Research has shown that CBT is effective in addressing sleep problems associated with prolonged grief disorder. CBT also has been shown to be superior in long-term effects to supportive counseling in children and adolescents experiencing symptoms of prolonged grief disorder [502; 503].

Bereavement support groups can provide a useful source of social connection and support. They can help people feel less alone, thus helping to avoid the isolation that could increase the risk for prolonged grief disorder. Despite the existence of effective treatments, people experiencing prolonged grief disorder may not seek help. One study of 86 bereaved caregivers with symptoms of prolonged grief disorder found that only 43% accessed mental health services [504].

ASSESSING AND DIAGNOSING DEPRESSION IN SPECIAL POPULATIONS

Healthcare providers can create a more comfortable environment for a patient of another culture by acknowledging the impact of culture and cultural differences on physical and mental health [76; 77]. Symptom presentation is influenced by cultural factors, and in some cultures, depression and anxiety may be expressed through somatic symptoms, such as musculoskeletal pain and fatigue. Providers may consider starting the conversation with the patient by focusing on physical symptoms. The concept of depression also varies across cultures, and patients may not seek medical treatment unless symptoms manifest as psychosis, conversion disorders, or significant physical ailments [78].

Women with somatization are more likely to indicate interest in medication and their faith as sources for mental health care. However, ethnic differences tend to be very pronounced regarding medication preferences, with ethnic minority women showing less interest in medication than White individuals born in the United States [79].

Black/African Americans

In general, Black/African Americans are more likely than White Americans to seek help for psychologic distress in the primary care settings and are more likely to believe that mental health professionals can be helpful, but also are more likely to believe mental illness will improve on its own [80]. They tend to seek services later and, therefore, face worse outcomes [81]. When they perceive they need help for an emotional problem, African American women tend to prefer individual or group therapy over medication [79].

Latinx/Hispanic Americans

Latinx/Hispanic Americans often show psychologic distress differently, and assessment for depressive symptoms alone may not adequately capture their psychologic distress [82]. Latinx/Hispanic Americans may be more likely to seek treatment for depression in primary care settings, although cultural values may be inconsistent with accepting treatment [80; 83]. Latina women are more likely to express distress via depressive symptoms while Latino men are more likely to externalize distress [82]. When they perceive they need help for an emotional problem, Latina women tend to prefer individual or group therapy over medication [79].

Asian Americans

Asian immigrants, especially Chinese Americans, are less likely to use mental health services than other ethnic groups [84]. The discrepancy between aspiration and achievement may better predict psychiatric illness and emotional disturbance than socioeconomic status [85].

Older Patients

Major depression or persistent depressive disorder (dysthymia) with an age of onset after 60 years is referred to as late-onset depression. It is characterized by a greater presence of apathy and less lifetime presence of personality pathology than depression of earlier onset. Older patients tend to exhibit more vegetative signs and cognitive disturbance and complain less of dysphoria. In this population, major depression may be misattributed to physical illness, dementia, or the aging process itself [86]. Depression in the elderly is widespread, often undiagnosed, and usually untreated. Several factors contribute to missed diagnoses of depression in the elderly, including differences in presenting symptoms, stereotyping, provider and organizational barriers, and polypharmacy [21].

Differences in Symptom Presentation

While DSM-based epidemiology studies suggest that the frequency of MDD declines with age, symptom-based assessment studies show increased rates of depression in older adults, especially women [21]. Older adults are less likely than younger adults to report feelings of dysphoria such as sadness, unhappiness, or irritability, suggesting that the standard diagnostic criteria for depression may be more difficult to apply to older adults or that older adults are disinclined to disclose such feelings [86; 87].

Similar to other subgroups, older adults with depression often present with nonspecific somatic complaints such as insomnia, appetite disturbances, lack of energy, fatigue, chronic pain, constipation, and musculoskeletal disorders [21]. Stigma also contributes to the denial among elderly patients of the psychologic symptoms of depression and refusal to accept the diagnosis. This appears to be particularly the case with older men, who also have the highest rates of suicide in later life [86; 88].

Provider-Related Factors

Provider-specific factors contributing to under-detection and under-treatment of depression include reluctance to inform older patients of a depression diagnosis due to uncertainty over the diagnosis and proper treatment, reluctance to stigmatize, concern regarding medication interactions, lack of access to psychiatric care, and doubts regarding treatment effectiveness and cost-effectiveness [89]. Additional factors are physician overconfidence in their ability to diagnose, treat, and manage depression in the absence of sufficient training and education and a presumption (based on their familiarity with the patient) that they have nothing new to learn about the patient [89; 90; 91].

Stereotyping

Healthcare professionals are not immune from harboring the stereotypes of the elderly often found among society in general. These can include attitudes that a depressive response to interpersonal loss, physical limitation, or changing societal role is an inevitable and even normal aspect of aging [89; 92; 93; 94]. The elderly may view their suicidal thoughts as age-appropriate [91]. When held by patients and family members, these erroneous beliefs can lead to under-reporting of symptoms and lack of effort on the part of family members to seek care for patients [93; 94]. When held by clinicians, these beliefs can result in delayed or missed diagnoses, less effective treatment, or suicide in the elderly patient. Studies have shown that a great majority of geriatric suicide cases have visited a physician within one month of their suicide [89; 91].

Systemic Barriers

The healthcare system itself has increasingly restricted the time allocated for patient care, forcing mental health concerns to compete with general medical conditions for provider attention. Primary care providers often report feeling too time-pressured to investigate depression in older patients [95].

Polypharmacy

First-episode depression in elderly patients may have an undiagnosed neurologic or other medical disorder etiology. Because some medications, such as beta-blockers, can precipitate depression in the elderly, consideration should be given to the potential role of medication side effects, particularly because this population is likely to be taking many different medications [22].

Women

As noted, women have a higher lifetime prevalence of depression and are particularly vulnerable during their childbearing years [11]. In one study, depressed women were found to mention mental symptoms when visiting a primary care provider for medical concerns (e.g., respiratory infection), giving practitioners clues as to their mental state that were not often explored [96]. Primary care providers should be alert to these clues, and screen and follow up with these women, as appropriate.

When depression develops during pregnancy, the course and presentation of the disease is often unique [19]. It is important that perinatal depression be identified and treated as early as possible to minimize the risks to the mother and fetus. Screening during the antepartum and postpartum periods should focus on signs and symptoms experienced in the previous week, utilizing a tool designed specifically for this population (e.g., the Edinburgh Postnatal Depression Scale) [97].

Children

Depression does develop in children, in some cases at a young age, and the long-term effects can be significant even after resolution of depressive symptoms [97]. There are several inherent barriers in the accurate assessment of younger children, including limited cognitive, language, and reading abilities [98]. For this reason, multiple "informants" are used to gain a clear clinical picture; however, it is important to remember that the child has the greatest knowledge regarding his or her own internal state. Several screening tools have been developed specifically for children and adolescents, but these are generally recommended for those 7 years of age and older [99; 100].

Lesbian, Gay, Bisexual, and Transgender Individuals

Some depression risk factors occur with greater frequency in gay, lesbian, bisexual, transgender, and other gender and sexual minority (LGBT+) communities, including family rejection, ostracism, bullying and peer victimization, and negative self-image, and depression is more common in this group than in the general population [101; 102]. However, there is some evidence that available screening tools may overestimate the incidence of mental disorders among LGBT+ patients [103]. Because the risk of suicide is high in this population, any possible depressive signs or symptoms should be fully explored.

DIFFERENTIAL DIAGNOSIS

Because depression can be a manifestation of other psychiatric conditions, substance use disorders, CNS disorders, general medical conditions, or medication side effects, a differential diagnosis should be performed to rule out other conditions that may account for the depression. MDD can co-occur with any medical condition, but depression can also be a biologic manifestation of certain neurologic and medical conditions. In these cases, primary depression is ruled out. Considerations for the conditions discussed in the following section should be made in the differential diagnosis [10; 22; 104].

CNS Conditions

A broad range of CNS processes and conditions can produce changes in mood, cognition, and behavior that resemble MDD. These include Alzheimer disease, Parkinson disease, Huntington disease, multiple sclerosis, stroke, and seizure disorders; neoplastic lesions of the CNS; inflammatory conditions such as systemic lupus erythematosus; sleep disorders, particularly obstructive sleep apnea; and infectious diseases such as syphilis, Lyme disease, and human immunodeficiency virus (HIV) encephalopathy.

Pharmacologic Agents

Medications that can induce mood changes include antihypertensive medications, steroids, medications that affect sex hormones, H2 histamine blockers, sedatives, muscle relaxants, appetite suppressants, and cytotoxic chemotherapy agents. Patients taking several medications are at increased risk.

Endocrine Disorders

Several endocrine disorders, including Addison disease, Cushing disease, hyper- and hypothyroidism, prolactinomas, and hyperparathyroidism, have been linked to symptoms of depression. Treatment of the underlying disease should alleviate depressive symptoms.

Other Psychiatric Conditions

Depressive symptoms or mood disturbance can be due to psychiatric conditions other than MDD. Intoxication or acute withdrawal associated with alcohol and almost all recreational drugs can disrupt mood, cognition, and behavior. Furthermore, depressive symptoms may be a phase of bipolar disorder. It is important to distinguish bipolar from unipolar depression, as treatment decisions are based on this distinction. Assessment should always involve inquiry about manic or hypomanic episodes, using the following DSM-5-TR criteria for bipolar disorder [10]:

- A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least one week and present most of the day, nearly every day (or any duration if hospitalization is necessary)
- During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree and represent a noticeable change from usual behavior:
  - Inflated self-esteem or grandiosity
  - Decreased need for sleep
  - More talkative than usual or pressure to keep talking (pressured speech)
  - Flight of ideas or subjective experience that thoughts are racing
  - Increase in goal-directed activity or psychomotor agitation
  - Excessive involvement in pleasurable or hedonistic activities with a high potential for painful consequences
- The mood disturbance sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features
- The episode is not attributable to the physiologic effects of a substance (e.g., an illicit drug, a medication, other treatment) or to another medical condition

These criteria constitute a manic episode. At least one lifetime manic episode is required for the diagnosis of bipolar I disorder.

Other psychiatric conditions with similar presentation to MDD include seasonal affective disorder, persistent depressive disorder, anxiety disorders, eating disorders, and personality disorders, especially borderline personality disorder. Many patients with MDD who appear labile, demanding, or pathologically dependent look dramatically different after the depressive episode has been treated adequately.

COMORBID CONDITIONS

Additional psychiatric disorders are present in many patients with MDD. Comorbidity rates differ between studies conducted with community compared with clinical populations. However, the most commonly occurring psychiatric comorbidities and their rates of occurrence in persons with MDD are [22; 105; 106; 107; 108]:

- Generalized anxiety disorder (62%)
- Social phobia (52%)
- Post-traumatic stress disorder (PTSD) (50%)
- Panic disorder (48%)
- Specific phobia (43%)
- Obsessive-compulsive disorder (42%)
- Any personality disorder (30%)
- Impulse control disorders (30%)
- Substance use disorders (24%)
- Borderline personality disorder (10% to 15%)

In addition, depression and certain medical conditions co-occur at very high rates. One large clinical trial found that depressed study participants had an average of 3.3 general medical conditions, including chronic pain, diabetes, cancer, HIV, Parkinson disease, and cardiovascular disease [109]. Medical comorbidity is highest among the elderly, with very high rates of depression found in patients with stroke (30% to 60%), coronary artery disease (up to 44%), cancer (up to 40%), Parkinson disease (40%), and Alzheimer disease (20% to 40%). The recurrence rate of MDD in the elderly is also extremely high, at roughly 40% [18].

Pseudodementia

Cognitive impairment often accompanies MDD. Some patients have both MDD and dementia, while others have cognitive impairment that is secondary to MDD, termed pseudodementia. Pseudodementia should resolve when MDD is successfully treated. Several clinical features help differentiate pseudodementia from true dementia. When performing cognitive tasks, pseudodemented patients generally exert relatively less effort but report more incapacity than demented patients. In the latter group, especially in the advanced stages, patients typically neither recognize nor complain of their cognitive failures, as insight is impaired. In contrast, pseudodemented patients often vehemently complain that they cannot think or remember clearly. Pseudodementia also lacks the signs of cortical dysfunction (e.g., aphasia, apraxia, agnosia) that are seen in degenerative dementia. It is essential that individuals with MDD-related cognitive disturbance not be misdiagnosed and subsequently denied aggressive treatment [22].

INITIAL TREATMENT OF DEPRESSION

Although the DSM-5-TR criteria require the presence of five of nine symptoms for MDD diagnosis, significant impairment in functioning can occur with as few as two symptoms [10; 110]. Therefore, the goal of treatment should be to achieve remission, to reduce relapse and recurrence, and to return patients to their previous level of occupational and psychosocial function. Remission is defined as the absence of depressive symptoms, response is defined as a 50% or greater reduction in symptoms, and partial response is defined as a 25% to 50% reduction in symptoms [21; 111].

An estimated 70% to 80% of antidepressants are prescribed in primary care, making it critical that clinicians understand their use and have a system that supports best practices [21]. However, evidence suggests that nonpsychiatric practitioners underdiagnose and undertreat depressive illnesses [43; 112]. Primary care clinicians who diagnose a patient with MDD face several challenges in achieving remission in the patient. These include time constraints on the treatment of a time-intensive disorder; potential comorbidities; lack of training on differential diagnoses; initial patient presentation for a medical and not a psychiatric problem; potential for poor adherence to treatment; unavailability of psychotherapy in many primary care clinics; potential discomfort among primary care providers in providing nonmedical, psychologic care; and patient expectation of a "quick fix" [43].

INITIAL COMMUNICATION WITH THE PATIENT

Patient Education

An essential aspect of treating major depression is the active engagement of patients and their families during the process. Engagement is the foundation for communication between providers and patients, and at the time of diagnosis, patient education represents a useful and important topic of communication. Patient education is also important to help counter the negative effects of pessimism, low motivation, low energy, social isolation, and guilt on treatment engagement and adherence [21; 22].

Diagnosis, prognosis, and treatment options should be addressed in patient education, which should also include a discussion of the costs, duration, side effects, and expected benefits of treatment. Patients should be reassured that depression is a medical condition, not a character defect, and recovery is the rule, not the exception [21; 22]. Treatment is effective for many patients, and it is important to stress the treatment goal is complete remission—not just getting better but staying well. However, the risk of recurrence is high (50% after one episode, 70% after two episodes, and 90% after three episodes),

and patients and family members should be alert to early signs and symptoms of depression recurrence and seek treatment as soon as possible if depression returns [42]. Clinicians should include the following topics related to treatment and follow-up in discussions with the patient before directly addressing specific therapy options [21; 22]:

- The causes, symptoms, and natural history of major depression
- Treatment options and the process of finding the best fit for each patient
- Information on what to expect during the course of treatment
- How to monitor symptoms and side effects
- The desired follow-up protocol, such as office visits and/or telephone contacts
- Early warning signs of relapse or recurrence
- The duration of treatment
- Communication with the provider
- The frequency of visits
- Patient expectations and beliefs in the controllability of their depressive symptoms

Patient Self-Management

Self-management refers to patient ability to manage treatment, lifestyle modifications, and associated physical and psychosocial challenges necessary to better ensure recovery from depression. Supported self-management typically includes action planning to change behavior. Techniques include behavioral activation, communication skills, emotion coping skills, patient education, healthy lifestyle, relapse-prevention planning, skill development, and self-monitoring. Effective self-management reduces patient reliance on healthcare providers and increases empowerment and self-efficacy [62; 113].

Behavioral Activation

Patients can be instructed to increase their daily involvement in pleasant activities and positive interactions with the environment as one of the aspects of their overall recovery plan [114]. Behavioral activation is appealing to patients in that it is simple and easily taught, effective in reducing milder depression, and can be continued following the conclusion of therapy. Behavioral activation can also be used in difficult-to-treat populations, such as depressed dementia patients. Among the elderly, regular outings and get-togethers, participation in a senior day care program, or available nursing home activities can reduce depression [21; 115; 116]. Results of a 2010 meta-analysis suggest that among patients with mild or subclinical depression, antidepressants may be no better than placebo, and that behavioral activation plus lifestyle modifications alone may offer sufficient symptom reduction [117].

Physical Activity

A robust body of evidence indicates that physical activity at a dose consistent with public health recommendations can lessen or alleviate symptoms of depression. Exercise therapy is very beneficial to patients with major depression, but the exercise must be continued over time to provide maximum benefit. Greater antidepressant effects occur when training continues beyond 16 weeks. Walking is a good initial option for many patients, and physically healthy adults should be encouraged to set a goal of 30 minutes of moderate-intensity aerobic exercise, three to five days per week [21].

DEVISING A TREATMENT PLAN

The two primary treatment options for most patients with MDD are psychotherapy and pharmacotherapy [111]. Evidence-based guidelines recommend that the process of treatment selection involve shared decision making between provider, patient, and family members, and that the values, priorities, and goals of the patient be included in discussions of risks and benefits of treatment options [118]. Ongoing communication with other providers involved in the care of a patient is essential for coordination and monitoring and can involve different care providers in the same primary care clinic or the primary care provider and therapist or psychiatrist [22].

Combining pharmacotherapy and psychotherapy treatments should be considered for patients with MDD when practical, feasible, available, and affordable. Both approaches combined show better outcomes than either as monotherapy. When unable to combine therapy because of patient preference or problems with availability or affordability, consider psychotherapy when the presentation is mild-to-moderate, and antidepressants when depression is severe or chronic [21]. Patients with MDD with psychotic features should receive an antipsychotic and an antidepressant medication or electroconvulsive therapy (ECT). Lithium can be added in patients unresponsive to antipsychotic/antidepressant therapy [22]. Other specific factors should be considered in treatment planning, including the presence of substance abuse, specific features, and other comorbid disorders. If a patient displays signs of potential suicide, increasing the treatment intensity, including hospitalization if needed, should be considered, and pharmacotherapy and psychotherapy should both be provided [22].

Alcohol or Substance Abuse/Dependence

With active substance abuse, detoxify the patient before antidepressant initiation when possible. Identifying patients who require antidepressants following the initiation of abstinence is difficult, because ongoing substance abuse can cause or amplify depressive symptoms that will dissipate with abstinence. Factors suggestive of benefit from early medication initiation include a family history of MDD, patient history of depression preceding alcohol or other substance abuse, or a history of significant depression during periods of abstinence. Use of some drugs of

abuse, especially stimulants, may create a toxic interaction with monoamine oxidase inhibitors (MAOIs), and benzodiazepines and other sedative-hypnotics should be used with great caution, except as part of a detoxification regimen [22].

Specific Features

As discussed, patients with MDD may present with features that specify the current episode as catatonic, melancholic, or atypical. Rapid alleviation of potentially life-threatening catatonia in patients with MDD with catatonic features may be necessary with intravenous lorazepam or amobarbital. ECT should be used immediately in unresponsive patients. Initiation of antidepressant medication should also begin, and catatonic patients given antipsychotic medication should be monitored for neuroleptic malignant syndrome [22].

Many treatment studies in symptom-based MDD subtypes (e.g., melancholic, atypical, anxious depression) have compared an active drug to placebo. Some report efficacy, but few have evaluated preferential subtype response [119; 120].

Comorbid Psychiatric Disorders

Both depressive and anxiety symptoms respond to antidepressant medication treatment, although SSRIs and TCAs may initially worsen anxiety symptoms. Benzodiazepines may be needed as short-term adjunctive therapy but should not be used as monotherapy. Clomipramine and SSRIs are efficacious in managing obsessive-compulsive symptoms, and all antidepressants should be initiated at a low starting dose [22].

Patients with MDD and comorbid personality disorders, especially borderline personality disorder, poorly respond to standard antidepressants, and MAOIs should not be used in patients with borderline personality disorder [22]. Psychodynamic psychotherapy may be beneficial in modifying the personality disorder in selected patients, although antisocial personality traits often interfere with treatment adherence and the psychotherapeutic relationship [22]. Other evidence suggests that comorbid personality disorders in patients with depression interfere with treatment response to interpersonal psychotherapy but not cognitive-behavioral therapy (CBT) [121].

Eating disorders can co-occur with depression. CBT is suggested in patients with bulimia nervosa; other effective therapies include interpersonal therapy, group therapies, family therapy, and SSRIs. Bupropion should be avoided due to lowered seizure threshold, and ECT has not been shown effective [22].

If depression is identified as seasonal affective disorder, bright-light therapy is recommended as first-line therapy and can be used adjunctively with antidepressants in more severe cases. The entire range of MDD treatments may also be used for seasonal affective disorder, either combined with, or in place of, bright-light therapy [22].

Persistent Depressive Disorder and Pseudodementia

Antidepressants appear to benefit some patients with persistent subthreshold depressive symptoms (dysthymia) but lack benefit in patients with recent-onset subthreshold depressive symptoms. No clear advantage has been shown among specific antidepressants, and psychotherapy should be considered [122; 68]. For patients with persistent subthreshold depressive symptoms or depression with mild-to-moderate severity, consider an antidepressant or CBT, interpersonal therapy, or behavioral activation [68]. Unlike true dementia, cognitive impairment in pseudodementia is secondary to MDD, and should resolve with adequate antidepressant or ECT response [22].

Demographic and Psychosocial Factors Influencing the Treatment Plan

Female Sex

Some women experience mood fluctuation with gonadal hormone levels, and assessment should include a detailed assessment of mood changes across the reproductive life history. Potential drug-drug interaction should also be considered when selecting an antidepressant in women taking oral contraceptives. In perimenopausal women, SSRI and SNRI antidepressants are useful in ameliorating depression as well as in reducing somatic symptoms such as hot flashes [22].

Major Psychosocial Stressors

An MDE may follow an adverse life event, often surrounding the loss of an important relationship or life role. Antidepressant treatment decisions for MDE following such events do not differ from other contexts, but the influence of past and current psychosocial stressors on MDE severity should be considered. Adding a psychologic treatment to medication may be particularly useful [22]. Antidepressant medications and/or psychotherapy should be used in prolonged reaction to relationship loss with significant functional impairment, and some patients may benefit from bereavement support groups [22].

A history of early-life trauma, such as physical/sexual abuse or parental loss or abandonment, should be considered in treatment selection. A study of 681 patients with chronic MDD found that among patients with childhood trauma, CBT was consistently more effective than antidepressant monotherapy, and that combining both therapies had no significant advantage over CBT monotherapy [123]. Remission was estimated to be twice as likely with psychotherapy than antidepressants, with special benefit noted in patients with early parental loss. These results suggest a preferential response to psychotherapy in patients with chronic MDD and a history of childhood trauma [123].

An ongoing family stressor can interfere with treatment response. Ambivalent, abusive, rejecting, or highly dependent family relationships can influence development or persistence of MDD. Such families should be evaluated for family therapy, which may be used in conjunction with individual and pharmacologic therapies [22].

Other Psychosocial Factors

Psychosocial stressors such as housing, food, childcare, transportation, employment, immigration status, and financial stability may be more prevalent in certain populations and should be considered during treatment planning [124]. Also, financial factors such as insurance coverage or generic versus brand name medications can affect treatment adherence. Among low-income minority women in the United States, availability of childcare and transportation are associated with significant improvement regardless of treatment modality. Medication noncompliance rates are higher in intercultural settings due to cultural expectations and communication problems [21; 125].

Cultural Factors

Essential to effective diagnostic assessment and clinical management of depression is an understanding of the cultural context of a patient's illness experience. Culture is the systems of knowledge, concepts, rules, and practices that the patient has learned over time and includes language, religion and spirituality, family structures, life-cycle stages, ceremonial rituals, customs, and moral and legal systems [10].

Ethnic minority and immigrant patients can experience many barriers to accessing mental health services, including stigma, deficits in knowledge/understanding, economic hardship, and language barriers [126]. Clinicians should take steps to address their own cultural competency when working with minority patients and ensure that all communications are clear and thorough, utilizing an interpreter when necessary. Different beliefs, values, and terms for depression will impact the perceived effectiveness of treatments. In addition, some cultures may be more likely to utilize alternative treatments (e.g., saffron) [126].

Older Age

The same factors used in therapy selection with younger patients also apply to the elderly, although treatment response may take longer to achieve [22]. The starting dose of pharmacotherapy and rate of dose escalation should be carefully considered, as the elderly are more susceptible to medication side effects, especially hypotension and anticholinergic effects [22]. Weight loss may be a concern for some older patients, who may benefit from medication that promotes weight gain [21].

The collaborative care approach with the elderly involves a treatment team composed of a depression care manager, primary care physician, and psychiatrist who provide a tailored approach to meet individual patient's needs and preferences. This approach is based on education, behavioral activation, antidepressants, brief problem-solving therapy, and relapse prevention [127]. Collaborative care has demonstrated considerably greater and more sustained improvement of depressive symptoms in the elderly than usual care [128].

Family History

A family history of bipolar disorder or acute psychosis indicates the need to monitor the patient for signs of bipolar disorder and treatment-emergent mania. A family history of recurrent MDD increases the likelihood of recurrent episodes and underscores the importance of maintaining treatment response. A family member with positive treatment response to a specific antidepressant offers important information to guide antidepressant selection [22].

Comorbid Medical Conditions

As with psychiatric conditions, comorbid medical conditions can impact the treatment plan for patients with depression. Pharmacologic agents should be chosen carefully in these patients due to the increased risk for adverse events and drug-drug interactions, and the following considerations are suggested [22]:

- Hypertension or cardiac conditions: Monitor vital signs and cardiac rhythm when treating with TCAs, SNRIs, or antidepressants with anticholinergic effects.
- Seizure disorders: Use with caution antidepressants that lower the seizure threshold, such as bupropion, clomipramine, and maprotiline.
- Parkinson disease: Serotonergic agents may worsen symptoms, and bupropion may benefit the illness but worsen psychosis if present. Selegiline may interact with L-DOPA, an agent used in the treatment of Parkinson disease.
- Obesity: Monitor for weight gain with most antidepressants.
- Sleep apnea: Choose an antidepressant with little daytime sedation.
- HIV infection: Carefully consider the potential drug-drug interactions between psychotropics and antiretrovirals.
- Chronic pain: SNRIs and TCAs are preferred over SSRIs and MAOIs.

OPTIONS FOR INITIAL THERAPY

In mild-to-moderate depression, psychotherapy can be equally as effective as medication, although with severe depression, antidepressant medication is usually necessary [129; 130]. Psychotherapy can significantly reduce symptoms, restore psychosocial and occupational functioning, and prevent relapse in patients with major depression [131]. It is especially useful in addressing the psychosocial stressors and psychologic factors that impact the development or maintenance of depressive symptoms [22]. Support and education in the primary care setting are critical to improving patient adherence and follow-through with treatment. Patient factors such as the nature and duration of depressive symptoms, beliefs and attitudes toward psychotherapy, and early-life experiences (e.g., history

of trauma) contribute to psychotherapy treatment response [22; 132]. Patient expectations as to the outcome of therapy, particularly the expectation that treatment will lead to an improvement in symptoms, is linked to favorable therapeutic outcomes [133]. Because antidepressants and psychotherapy are both effective, careful consideration of patient preference for mode of treatment is appropriate, and a referral for psychotherapy should be given whenever psychologic or psychosocial issues are prominent or if the patient requests it [134; 135; 136].

Phases of Treatment

With the traditional three-phase model of acute, continuation, and maintenance, the distinction between continuation and maintenance phases was based on a theoretical difference between relapse (symptom recurrence before resolution of current episode) and recurrence (symptoms that constitute a new episode, after recovery from previous episode) [137; 138]. However, studies have highlighted the lack of evidence to support distinct demarcations between relapse and recurrence episodes, and a two-phase model (acute and maintenance) is now recommended [62; 139].

Acute Phase

The primary goals for the initial 8- to 24-week acute treatment phase are symptom remission, meaning that signs and symptoms of depression are absent or nearly so, and restoration of psychosocial functioning. Full symptom remission is important because residual depressive symptoms are risk factors for relapse and negative predictors of long-term outcomes. Clinicians can help patients achieve these goals through establishing a therapeutic alliance, providing patient education and self-management support, selecting appropriate treatment, and monitoring the patient for treatment response, side effects, functional status, adherence, risk of harm to self or others, and co-occurring psychiatric and medical comorbidities [43; 62; 140; 141].

Maintenance Treatment Phase

Preventing recurrence is a key goal during the maintenance phase of 6 to 24 months or longer. Clinicians should focus on healthy life strategies, personality vulnerabilities, long-term self-management, and clinical strategies to reduce recurrence and help the patient return to full functioning and quality of life. For a significant proportion of patients with MDD, maintenance pharmacologic, psychologic, complementary and alternative medicine, and neurostimulation treatments play a role in preventing recurrence. Other key clinician activities include treating comorbidities and monitoring for recurrence [62; 139; 142].

Treatment Duration

As noted, the antidepressant dose that leads to a satisfactory acute therapeutic response should be maintained during long-term treatment to prevent relapse and recurrence of depression [143; 144]. Historically, practice guidelines recommended initial treatment continuation for 6 to 12 months, but this is not supported by evidence and discontinuation decisions should not be based on treatment duration alone [145]. The two most important factors are maintaining current response and preventing relapse. Risk factors associated with chronic MDD or recurrent MDE include [62]:

- Earlier age of onset
- Severity of the initial episode (e.g., higher number of symptoms, suicidal ideation, psychomotor agitation)
- Greater number of previous episodes
- Disrupted sleep-wake cycle
- Comorbid psychopathology
- Family history of psychiatric illness
- Presence of negative cognitions
- High neuroticism
- Poor social support
- Stressful life events

The duration of untreated MDD is strongly linked to antidepressant nonresponse [62; 146].

When patients with these characteristics show substantial response or remission, the focus is helping the patient maintain their level of treatment response. When antidepressants are discontinued, have a contingency plan in place for prompt intervention if relapse occurs [38]. Early antidepressant discontinuation usually results from side effects, lack of improvement, inadequate education about the illness, failure to engage the patient during follow-up, and psychosocial factors [147; 148].

PSYCHOTHERAPY

The objective of psychotherapy (sometimes referred to as psychologic or psychosocial therapy) is to change thinking and behavior patterns, which in turn reduces emotion and stress reactivity in limbic regions and increases connectivity in limbic-cortical pathways and inhibitory control functions of prefrontal cortical regions [149]. Psychosocial treatments are preferred by many individuals with MDD, and psychotherapies can be sequenced as add-on approaches for insufficient initial antidepressant response or used as initial treatment, with antidepressants reserved for poor response to psychosocial treatment. However, many patients with more severe depression or cognitive impairment will require some degree of pharmacologic treatment to engage and maintain participation in psychotherapy [150].

Cognitive-Behavioral Therapy

CBT is a structured, circumscribed psychologic intervention that is grounded in the cognitive-behavioral model of affective disorders, which posits that irrational beliefs and distorted attitudes toward the self, the environment, and the future perpetuate depressive affects and compromise functioning [22]. When CBT is used for depression, the patient works collaboratively with the therapist to identify maladaptive or self-defeating thoughts, beliefs, and interpretations and their impact on current symptoms, feelings states, and/or problem-

solving abilities. Therapeutic techniques include patient education and patient-therapist collaboration to choose goals, identify unhelpful thoughts, develop experiments to challenge the accuracy of such thoughts, and identify alternative beliefs through questions that explore beliefs that exacerbate depression. Treatment incorporates structured practice outside of therapy, with scheduled activities, mood tracking, thought recording and challenging, and interpersonal skills practice. CBT can be delivered via computer software and/or by group therapy format [64].

Mindfulness-Based Cognitive Therapy

Mindfulness-based cognitive therapy integrates standard CBT with mindfulness-based skills, including mindfulness meditation, guided imagery, experiential exercises, and other techniques. The goal is to assist patients with MDD in recognizing, detaching from, and accepting negative thoughts or affect while embracing self-compassion, without necessarily attempting to change them. With practice, patients can become more detached from dysfunctional thoughts by observing them as objects [64].

Interpersonal Psychotherapy

Derived from attachment theory, interpersonal psychotherapy focuses on improving interpersonal functioning and exploring relationship patterns. It addresses the connection between patients' feelings and current relationship difficulties by targeting four primary areas: interpersonal loss, role conflict, role change, and interpersonal skills [64].

Short-Term Psychodynamic Psychotherapy

Derived from longer-term psychoanalysis and psychodynamic psychotherapy, short-term psychodynamic psychotherapy assists patients in gaining insight into unconscious conflicts as they manifest in daily life and relationships, including the therapeutic relationship (i.e., transference). This approach considers these conflicts to originate in the past, usually childhood relationships to parental figures. Patients gain insight into and work through such conflicts by exploring their feelings and therapist interpretation [64].

Marital/Family Therapy

Marital and family problems are common in mood disorders, and can predate, perpetuate, or develop as consequence to the mood disorder. Marital/family therapy approaches effective in depression treatment include behavioral approaches, problem-focused approaches, and strategic marital therapy. Marital/family therapy is a helpful adjunct to medications and hospitalization in severely ill patients [22].

Complicated Grief Therapy

Complicated grief therapy involves history-taking, psychoeducation about complicated grief and its treatment, work with memory and pictures, and imagined conversations with the deceased, over a 16-week period. In one study, adults with complicated grief were randomized to combinations of complicated grief therapy, citalopram, or placebo. Complicated grief was very much improved with complicated grief therapy; adding citalopram had no further benefit. Depressive symptoms showed greater decrease with citalopram added to complicated grief therapy; citalopram response at 20 weeks was comparable to placebo. Suicidal ideation rates showed greatest reduction with complicated grief therapy [75].

Problem-Solving Therapy

Problem-solving therapy is a time-limited, structured intervention involving therapist-patient collaboration to identify and prioritize problems; break problems down into specific, manageable tasks; problem solve; and develop appropriate coping behaviors for problems. It was developed to specifically address social problem-solving deficits common in chronic depression [151; 152]. Problem-solving therapy is designed for use in primary care settings [153; 154].

Psychotherapy Treatment Recommendations

For patients with moderate-to-severe depression, a combination of antidepressant medication and CBT or interpersonal therapy should be provided. The choice of intervention should be influenced by the duration of the episode of depression and symptom trajectory, previous course of depression and treatment response, likelihood of adherence to treatment, any potential adverse effects, and individual treatment preference and priorities [68]. A 2017 evaluation of whether CBT response was influenced by baseline depression severity suggested that patients with MDD can expect as much benefit from CBT across the wide range of illness severity [155].

For patients with persistent subthreshold depressive symptoms or mild-to-moderate depression who decline an antidepressant, CBT, or interpersonal therapy, consider counseling. Short-term psychodynamic psychotherapy should be offered to patients with mild-to-moderate depression. Individual CBT is an option for patients who have either relapsed despite antidepressant medication or have a significant history of depression and residual symptoms despite treatment and are unable or unwilling to continue antidepressant treatment. Mindfulness-based cognitive therapy should be offered to patients who are currently remitted but have experienced three or more previous episodes of depression [68].

Psychotherapy is preferred as a first-line treatment for elderly patients because of potential increased toxicity and drug-drug interactions. The evidence does not support superiority of one psychotherapy modality over another in elderly patients with MDD [64].

PHARMACOTHERAPY

Treatment with antidepressant medications can involve dosage adjustments and/or trials of a different medication at some point to maximize response and minimize side effects [22]. Patient adherence to the medication regimen is essential in achieving the maximum clinical benefit. Strategies to enhance adherence are discussed below. Patient education regarding the treatment plan should include when and how often to take medication; the anticipated two- to four-week lag before

RECOMMENDATIONS FOR MDD SPECIFIERS AND DIMENSIONS	
Specifier or Dimension	**Recommended Agent(s)**
Anxious distress	Antidepressants with efficacy in generalized anxiety disorder (SSRIs, SNRIs, and bupropion comparable in efficacy)
Mixed features	Lurasidone Asenapine Quetiapine Aripiprazole Ziprasidone
Melancholic features	TCAs SNRIs
Atypical features	MAOIs (superior to TCAs in older studies)
Psychotic features	Antipsychotic-antidepressant combinations
Catatonic features	Benzodiazepines
Seasonal pattern	SSRIs Agomelatine Bupropion Moclobemide
Cognitive dysfunction[a]	Vortioxetine (highest efficacy) Bupropion Duloxetine Modafinil Moclobemide
Sleep disturbance[a]	Agomelatine (highest efficacy) Mirtazapine Quetiapine Trazodone (high rates of somnolence and daytime sedation)
Fatigue[a]	Bupropion (highest efficacy) SSRIs
Low energy[a]	Duloxetine
Neuropathic pain and fibromyalgia[a]	Duloxetine (highest efficacy) Amitriptyline Other SNRIs
[a]Clinical dimension not recognized in the DSM-5-TR.	
Source: [158; 159; 160]	*Table 1*

beneficial effects may be noticed; the need to continue medication even after feeling better; what to do if problems arise; and the importance of tapering antidepressants before discontinuing them [22]. Providers should closely monitor patients for worsening depressive symptoms and emergent suicidality; appropriate intervention includes stopping or modifying the drug therapy or hospital admission [21]. Providers should instruct patients and caregiver(s) to be alert for emerging agitation/irritability, suicidality, and worsening depression, and to report this immediately to a healthcare provider [21].

An antidepressant medication is indicated for initial treatment of patients with mild to moderate depressive disorder. The effectiveness of antidepressants is comparable between and within classes of medications, including TCAs, SSRIs and other second-generation agents (e.g., SNRIs, bupropion), and MAOIs. Selection of a second-generation antidepressant is often recommended for initial treatment due to quality of published data, side effect profile compared to TCAs and MAOIs, and relative safety [21; 22; 156]. The choice of medication should be based on the following considerations: patient preference; nature of prior patient or family member response to medication; safety, tolerability, and anticipated side effects; co-occurring conditions and potential drug-drug interactions; cost [21; 22]. For most patients, a SSRI, a SNRI, mirtazapine, or bupropion is optimal for initial therapy. The use of MAIOs should be restricted to patients who do not respond to other treatments [21; 22].

The three most distressing side effects for patients treated with antidepressants are sleep disturbance, sexual dysfunction, and weight gain [157]. Choice of medication should be guided by knowledge of comparative side effects and patient priorities; some patients will be more concerned about sexual side effects, while for others, nausea, sleep disturbances, or weight gain may be more distressing [64]. In addition, available evidence regarding the optimal pharmacotherapeutic selection for the treatment of dimensions of depression and DSM-5-TR specifiers should be considered (***Table 1***).

Selective Serotonin Reuptake Inhibitors

SSRIs are thought to act by inhibiting serotonin transporters (SERT) that reuptake serotonin (5-HT) into the presynaptic cell, increasing 5-HT in the synaptic cleft. SSRIs have advantages of low overdose lethality and better tolerability than first-generation antidepressants, which can improve adherence. SSRIs are particularly effective in patients with obsessive-compulsive symptoms but may initially worsen anxiety or panic symptoms [21; 22; 122]. This class includes the agents fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), fluvoxamine (Luvox) (off-label for MDD), citalopram (Celexa), escitalopram (Lexapro), and vortioxetine (Brintellix). Escitalopram may have fewer drug-drug interactions than other SSRIs, and fluoxetine may be a better choice in patients with poorer adherence due to its long half-life [21; 22; 122].

Common Side Effects

The most common side effects with SSRIs are gastrointestinal (nausea, vomiting, and diarrhea), activation/insomnia (restlessness, agitation, anxiety, akathisia, and sleep disturbances), sexual, headache, fatigue, and weight gain [21; 22; 122]. Many of these side effects dissipate over time. Sertraline is particularly associated with diarrhea, and paroxetine with weight gain [22; 122].

Multimodal Antidepressants

Vilazodone and vortioxetine are multimodal antidepressants that combine SSRI properties with other pharmacologic actions affecting monoamine and non-monoaminergic targets. Evidence does not suggest greater efficacy than SSRI/SNRIs, but these agents may improve tolerability or efficacy on specific clinical domains [161].

Vilazodone, approved in 2011, primarily acts as a SERT inhibitor and 5-HT1A receptor partial agonist, and modestly inhibits dopamine and norepinephrine transporters. This antidepressant may be most helpful in patients lacking response to initial SSRIs. Vilazodone must be taken with food, which increases its absorption and bioavailability by 72% [162; 163].

Vortioxetine, approved in 2013, acts through various serotonin receptors as an antagonist (5-HT3/7/1D), partial agonist (5-HT1B), or agonist (5-HT1A), and inhibits SERT. It also activates the glutamate system in the frontal cortex. Vortioxetine displays a specific clinical efficacy in the treatment of cognitive deficits associated with MDD. The most common side effects are nausea, vomiting, and constipation [161].

Serotonin-Norepinephrine Reuptake Inhibitors

SNRIs act by inhibiting the reuptake of the neurotransmitters serotonin and norepinephrine. This results in an increase in the extracellular concentrations of serotonin and norepinephrine and therefore an increase in neurotransmission [21; 22; 122]. Most SNRIs, including venlafaxine (Effexor), desvenlafaxine (Pristiq), levomilnacipran (Fetzima), and duloxetine (Cymbalta), are several-fold more selective for serotonin than norepinephrine.

Safety, tolerability, and side effect profiles of SNRIs resemble SSRIs, with the exception that the SNRIs have been associated (rarely) with sustained elevated blood pressure. SNRIs can be used as first-line agents, particularly in patients with significant fatigue or comorbid chronic pain, and have an important role as second-line agents in patients who have not responded to SSRIs [21; 22; 122].

Venlafaxine is especially beneficial in treating anxiety and panic attacks in patients with depression, and acts like an SSRI at lower doses (75 mg/day) but more like an SNRI at doses ≥150 mg/day [21; 22; 122].

Common Side Effects

SNRIs are associated with greater likelihood of increased pulse rate, dilated pupils, dry mouth, excessive sweating, and constipation [21]. Venlafaxine has a greater incidence of nausea and vomiting than SSRIs and may be associated with an increased risk for cardiovascular events [22; 122].

Tricyclic Antidepressants

TCAs are predominantly serotonin and/or norepinephrine reuptake inhibitors that act by blocking the serotonin transporter and the norepinephrine transporter, respectively, which results in an elevation of the extracellular concentrations of these neurotransmitters, and therefore an enhancement of neurotransmission. TCAs also have varying but typically high affinity for the H1 and H2 histamine receptors and muscarinic acetylcholine receptors. As a result, they also act as potent antihistamines and anticholinergics. These properties are generally undesirable in antidepressants, however, and likely contribute to their large side effect profiles [164].

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

TCAs are comparable in efficacy to SSRIs/SNRIs, but their side effect profile makes them seldom used as first-line therapy [21; 22; 122]. TCAs may initially worsen anxiety or panic symptoms. Due to side effect potential of cardiac arrhythmia, TCAs should be used very cautiously, if at all, in patients with

MAOI INTERACTION TO TYRAMINE CONTENT IN FOOD		
None to Little	**Moderate**	**Severe**
Avocados	Red wine	Aged cheeses
Bananas	White wine	Aged and fermented meats
Bouillon	Canned beer	Broad (fava) bean pods
Chocolate		Spoiled meats and fish
Fresh cheeses		Soy sauce
Fresh meats		Tap beer
Peanuts		Smoked or pickled fish
Soy milk		Sauerkraut
Yeast extracts		
Source: [166]		*Table 2*

heart problems. Secondary amine TCAs cause less orthostatic hypotension and sedation than tertiary amines, which should be avoided in elderly patients due to the risk for orthostatic hypotension, sedation, cognitive problems, and cardiac effects. The secondary amine nortriptyline is especially effective for elderly patients with moderate-to-severe depression. Clomipramine is particularly effective in patients with obsessive-compulsive symptoms [21; 22; 122].

Common Side Effects

Anticholinergic and antihistamine activity accounts for many side effects, including dry mouth, blurred vision, reduced gastrointestinal motility or constipation, urinary retention, cognitive and/or memory impairment, and increased body temperature [21; 22; 122]. Other side effects may include drowsiness, anxiety, emotional blunting (apathy/anhedonia), confusion, restlessness, dizziness, akathisia, hypersensitivity, changes in appetite and weight, sweating, sexual dysfunction, muscle twitches, weakness, nausea and vomiting, hypotension, tachycardia, and arrhythmia. Tolerance to side effects often occurs if treatment is continued. Side effects may also be less troublesome if treatment is initiated with low doses and gradually increased [164; 165].

Monoamine Oxidase Inhibitors

MAOIs inhibit monoamine oxidase (MAO), an enzyme that degrades and inactivates 5-HT, norepinephrine, and dopamine. This increases monoamine levels and activity. Earlier MAOIs were irreversible MAO inhibitors, deactivating the enzyme until slowly replenished over a two-week period [166; 167]. MAOIs includes phenelzine (Nardil), tranylcypromine (Parnate), isocarboxazid (Marplan), linezolid (Zyvox, Zyvoxam, Zyvoxid), moclobemide (Aurorix, Manerix), pirlindole (Pirazidol) (approved for use in parts of Europe), and selegiline (Deprenyl, Eldepryl, Emsam).

Most MAOIs appear broadly effective in a range of depressive and anxiety disorders and may be more effective than other antidepressant classes in MDD with pronounced anxiety or panic symptoms [21; 22; 122]. MDD with atypical features may preferentially respond to MAOIs over other antidepressant classes. Although effective, MAOIs are rarely the first- or second-line treatment choice due to serious side effect potential from medication interactions and dietary restriction. The selegiline transdermal patch (Emsam) used at the lowest strength (6 mg delivered over 24 hours) may lack the dietary restrictions required of oral MAOIs [168]. Moclobemide is a reversible inhibitor of monoamine oxidase type A, greatly improving its safety, including overdose safety (i.e., 20,000 mg ingestion was non-fatal). This drug lacks TCA side effects or SSRI/SNRI sexual side effects; improved libido, erection, or orgasm is more commonly reported [169; 170]. Moclobemide may be superior to other antidepressants in treatment-resistant depression [171]. This drug is approved for use in Canada and throughout Europe and Asia but is not available in the United States [169].

Common Side Effects

With oral ingestion, MAOIs inhibit the catabolism of dietary amines. When foods containing tyramine are consumed, the individual may suffer from hypertensive crisis (***Table 2***) [166]. If foods containing tryptophan are consumed, hyperserotonemia may result. The amount required to cause a reaction varies greatly from individual to individual and depends on the degree of inhibition, which in turn depends on dosage and selectivity.

MAOIs should not be combined with psychotropic drugs or with any other psychoactive substance except under expert care. This includes a wide range of prescribed, over-the-counter, and illicit drugs and nutritional supplements, such as St. John's wort. Common side effects include orthostatic hypotension, weight gain, sexual dysfunction, sedation, headache, and insomnia [166].

Atypical Antidepressants

The atypical antidepressants are diverse in monoamine activity and do not fit the profile of other classes. They include bupropion (Wellbutrin), nefazodone (Serzone), mirtazapine (Remeron), and trazodone (Desyrel). Nefazodone and trazodone block postsynaptic serotonin type-2 receptors and inhibit presynaptic serotonin reuptake. Bupropion inhibits activity of norepinephrine and dopamine transporters, and the active metabolite hydroxybupropion contributes to the drug's effects. Mirtazapine is a potent antagonist at 5-HT2, 5-HT3, alpha2, and H1 histamine receptors. As a group, these agents show low toxicity in overdose and may have an advantage over the SSRIs by causing less sexual dysfunction and gastrointestinal distress [21; 22; 122].

Each agent has apparent benefits and drawbacks, with some better suited for specific patient populations. Bupropion is associated with a risk of seizure at higher doses, especially in patients with a history of seizure or eating disorders, and should be used cautiously in anxious patients [21; 22; 122]. It may be more effective for atypical MDD than other antidepressants.

Mirtazapine can be very sedating and promotes appetite and weight increase, which in some patients may be desirable. It has a faster onset of action than fluoxetine, paroxetine, or sertraline, and may be superior to SSRIs in depression associated with severe insomnia and anxiety. Trazodone is also very sedating and is usually used as a sleep aid rather than as an antidepressant [21; 22; 122].

Common Side Effects

The side effects of atypical antidepressants vary considerably. With bupropion, the most common side effects are agitation, jitteriness, mild cognitive dysfunction, insomnia, gastrointestinal upset, and possible increased risk for seizures [122]. Patients taking mirtazapine may experience dry mouth, sedation, weight gain, and increased serum cholesterol [22]. Sedation is the most common side effect associated with trazodone, followed by cardiovascular side effects (such as orthostasis) and sexual side effects [22]. Finally, nefazodone is associated with sedation, dry mouth, nausea, constipation, orthostasis, visual alterations, and possible increased risk of hepatotoxicity have led to nefazodone being seldom prescribed [122].

CNS Stimulants

Although the role of psychostimulants for antidepressant monotherapy is very limited, they may have a role in the treatment of apathetic major depression in which apathy imperils adherence to treatment and self-care, in patients who cannot tolerate the side effects of standard antidepressants, in terminally ill and medically ill patients with depression, and in elderly patients with complicating medical conditions [10; 172; 173; 174].

This medication class includes amphetamine derivatives such as dextroamphetamine (Dexedrine, Adderal), methylphenidate (Ritalin), and modafinil (Provigil). Methylphenidate inhibits dopamine reuptake by its transporter and, to a lesser degree, norepinephrine reuptake. Dextroamphetamine increases cytosolic dopamine and norepinephrine by blocking vesicular sequestration of dopamine and norepinephrine through inhibition of vesicular monoamine transporter-2 activity [21; 22; 122].

Common Side Effects

In general, CNS stimulants are associated with side effects related to hyperarousal (e.g., agitation, aggression, tachycardia, restlessness, insomnia). Other potential side effects include headache, anorexia, nausea, and irritability [175]. Modafinil is associated with markedly lower subjective stimulation.

CNS stimulants are contraindicated in patients with a history of substance use disorder, with agitated states, and with moderate-to-severe hypertension [175]. In addition, patients who have initiated MAOIs within the last 14 days should not begin therapy with a dopamine agonist.

Pharmacotherapy to Improve Cognitive Dysfunction

Full functional recovery is the overarching therapeutic goal of MDD treatment. Cognitive symptoms of depression critically impact social, occupational, and physical functioning; often persist after mood symptoms have lessened or remitted; and elevate recurrence risk in remitted patients. Functional outcomes modestly correlate with mood symptom outcomes but are strongly influenced by persistent cognitive impairment [176; 177; 178]. Mood symptoms are a primary focus of depression assessment and treatment, and standard depression pharmacotherapies have minimal benefit on improving cognitive dysfunction.

Vortioxetine has demonstrated efficacy in improving multiple domains of cognitive function, including executive function, processing speed, attention, and learning/memory, independent of its effect on core mood symptoms [45; 179; 180]. Duloxetine can improve learning and memory in patients with MDD [181]. Lisdexamfetamine has some benefit in improving executive function, while single-dose modafinil (200 mg) significantly improved performance on tests of episodic memory and working memory in remitted MDD subjects without side effects [159; 182].

Potential Complications with All Antidepressants

Sexual Dysfunction

All commercially available antidepressants are associated with sexual side effects. SSRI/SNRIs show the highest rates of sexual dysfunction, including impaired sexual motivation, desire, arousal, and orgasm affecting men and women. Prescribing physicians greatly underestimate the prevalence and patient burden of sexual side effects from antidepressants and other medications [183]. Among antidepressants, prevalence rates

of sexual side effects are highest with venlafaxine and SSRIs; moderate with TCAs and MAOIs; low with bupropion, trazodone, nefazodone, mirtazapine, agomelatine, and vilazodone; and lowest with the reversible MAOI moclobemide [184; 185]. Compared to spontaneous patient reporting, systematic inquiry increases the rate of identifying sexual side effects by ≥60% [185].

Management of sexual side effects in men includes the use of phosphodiesterase-5 inhibitors such as sildenafil, vardenafil, tadalafil, and avanafil as first-line treatment or switching to bupropion [186]. In women, sexual side effect management considers symptoms, age, and potential hormonal contribution when peri- or post-menopausal.

Increased Suicidality

Several papers documenting an increased risk of suicidal thoughts and behavior with antidepressants, primarily SSRIs, have been published over the past decade. A review of the literature found that antidepressant use, including SSRIs, carried a small short-term risk of inducing suicidal thoughts and suicide attempts in persons younger than 25 years of age, with persons 30 to 40 years of age having a lower risk than those younger than 25 years. This risk should be balanced against the well-known beneficial effects of antidepressants that include reduced suicidal ideation and behavior, particularly in the long term. Clinical decision making should weigh the benefits and potential risks and strive to keep the potential risks of antidepressant treatment to a minimum [187; 188].

Discontinuation Symptoms

Antidepressant discontinuation (more appropriately termed withdrawal) symptoms are described by the FINISH mnemonic (flu-like symptoms, insomnia, nausea, imbalance, sensory disturbances, hyperarousal), may be experienced by up to 40% of patients when antidepressants are stopped abruptly, and may occur with any antidepressant [158; 189; 190; 191]. SSRI withdrawal symptoms are far more frequent with paroxetine. Common symptoms include dizziness, nausea, headache, confusion, low energy, weakness, sleep disturbance, flu-like symptoms, restlessness, agitation, anxiety, panic, anger, and irritability. Less common and more severe symptoms include electric-shock sensations, vertigo, paresthesia, intensified suicidal ideation, aggression, derealization, depersonalization, and visual/auditory hallucinations. Gradual tapering is a reasonable strategy but does not prevent the onset of SSRI withdrawal [192]. SSRI withdrawal syndrome is least likely with fluoxetine and vortioxetine [158].

Symptoms usually begin within five days of treatment cessation or occasionally during taper or after missed doses [193; 194]. Symptoms are usually mild and self-limiting but may also be severe and prolonged, particularly following abrupt withdrawal. Some symptoms occur more frequently with specific drugs, such as dizziness and electric shock-like sensations with SSRIs and sweating and headache with TCAs [189; 195]. Risk factors include taking antidepressants longer than eight weeks, development of anxiety symptoms during antidepressant initiation (particularly with SSRIs), use of other medications with CNS activity (e.g., antihypertensives, antihistamines, antipsychotics), and a history of previous discontinuation symptoms [195; 196]. Outpatients who discontinued escitalopram and developed a withdrawal syndrome (56%) had significantly higher mean escitalopram doses and higher plasma concentrations reflecting delayed clearance of escitalopram, than patients without withdrawal. Escitalopram treatment duration, age, and sex were unrelated to withdrawal risk [197].

Symptoms may be severe enough to interfere with daily functioning, and although a four-week taper is usually suggested, some patients may require longer periods, particularly with paroxetine and venlafaxine [198]. Treatment is pragmatic. If symptoms are mild, reassure the patient that this is a common occurrence and that the symptoms will pass in a few days. If symptoms are severe, reintroduce the original antidepressant or a replacement from the same class with a longer half-life, and taper gradually while monitoring for symptoms. Patients should be emphatically informed that the possible or actual emergence of discontinuation symptoms is not a manifestation of addiction to the antidepressant [68]. SSRI withdrawal can also be approached by switching to a course of fluoxetine, such as 10 mg for several weeks, which is slowly tapered and discontinued [22].

Extended-release venlafaxine has the most severe withdrawal syndrome of any antidepressant. In addition to serotonergic withdrawal symptoms, persistent visual images and sensory disturbances are frequently reported. Electrical shock-like sensations in the brain or the sensation of the brain shivering has also been described. This sensory disturbance, often accompanied by dizziness, headache, and disorientation, is distressing to patients and may persist for months after cessation of the drug [199; 200]. Other unexpected symptoms that may emerge include gait difficulties, delirium, suicidal ideation, hypomania, or mania. The usual onset of withdrawal is one to four days post-cessation or with dose reduction [201].

The origin and treatment of these highly distressing sensory symptoms are unknown, but case reports describe positive response to noradrenergic agents. Abrupt cessation of extended-release venlafaxine 37.5 mg led to sensations that "felt like the brain was shaking inside the skull," with anhedonia, anxiety, tinnitus, headache, nausea, and increased noise sensitivity. A trial of atomoxetine (40 mg/day), a norepinephrine transporter inhibitor, led to immediate improvement in "brain shivers" two to three hours from the first dose [199]. Post-cessation electric shock-like sensations and dizziness were greatly reduced by low-dose clonidine (0.05 mg twice-daily). These positive responses suggest an underlying noradrenergic rebound mechanism [200].

TREATMENT OF SIDE EFFECTS ASSOCIATED WITH ANTIDEPRESSANT USE	
Side Effect	**Treatment**
Orthostatic hypotension	Fludrocortisone Add salt to diet
Dry mouth	Pilocarpine oral rinse Gum and/or hard candy
Constipation	Hydration Bulk laxatives
Urinary hesitancy	Bethanechol
Visual changes	Pilocarpine eye drops
Sedation	Bedtime dosing Modafinil, armodafinil, methylphenidate
Insomnia	Morning dosing Trazodone or melatonin at bedtime
Myoclonus	Clonazepam
Seizures	Antiepileptic medication
Impaired sexual arousal, erectile dysfunction, orgasm dysfunction	Sildenafil Tadalafil Buspirone Bupropion Flibanserin
Hyperlipidemia	Statin medication
Akathisia	Beta-blocker Benzodiazepines
Diaphoresis	Terazosin Clonidine Benztropine
Weight gain	Exercise Other antidepressant with less weight promotion, if necessary
Source: [22]	*Table 3*

Medication Interactions

Most antidepressant drugs have clinically significant drug interactions and it is beyond the scope of this course to discuss all possible interactions. Practitioners are encouraged to consult references such as the Physician's Desk Reference or the American Hospital Formulary Service for information about adverse drug-drug interactions.

Strategies to Manage Side Effects

Research has found that prescribing clinicians consistently underestimate both the frequency of side effects and patient discomfort caused by them, with distress caused by blurred vision and constipation being the most underestimated [202]. The suggested management of many side effects consists of either reducing the dose or discontinuing the medication. However, several focused interventions for specific side effects can be implemented when patients are reluctant to discontinue or switch to another medication, when the side effect is mild-to-moderate in severity, or when there is evidence of treatment response (***Table 3***) [22].

ADDITIONAL CONSIDERATIONS WITH INITIAL THERAPY

Duration of Initial Treatment

Response trajectories are highly variable following antidepressant initiation for MDD. Some patients show robust improvements within one to three weeks, while others have a slower velocity of symptom change. A sizeable subgroup lacks response, and an underidentified subgroup worsens [150; 203].

In predicting substantive response or remission six to eight weeks after treatment initiation, symptomatic improvement by two to three weeks is a modest predictor, but minimal symptomatic improvement by two to three weeks is a far more robust negative predictor of poor or non-response that signals the need to optimize treatment intensity [150; 203; 204; 205].

From a clinical perspective, it is unrealistic to expect patients with MDD and minimal treatment response to continue with their antidepressant beyond two to four weeks. Integrating best evidence with pragmatism, intervention is recommended with insufficient outcome (symptom reduction ≤20%) after two to four weeks of treatment [62; 150]. With minimal improvement by two to four weeks, the recommended approach is to increase the dose, if the initial antidepressant is tolerated, or switch to another antidepressant if side effects are problematic [158].

Comparative Discontinuation Rates Due to Side Effects

A meta-analysis of randomized controlled trials involving second-generation antidepressants found that overall discontinuation rates did not differ significantly between SSRIs as a class and bupropion, mirtazapine, nefazodone, trazodone, and venlafaxine. The higher discontinuation rate of venlafaxine versus SSRIs due to side effects (11.5% vs. 8.5%) was balanced by lower discontinuation rates due to lack of efficacy (3.5% vs. 4.4%) [122].

Collaboration with Mental Health Professionals

Primary care providers should consider collaborating with behavioral healthcare providers when caring for patients with depression, especially in the following situations [21]:

- Patient request for psychotherapy
- Severe symptoms and impairment in patient
- High suicide risk
- The presence of other psychiatric condition (e.g., personality disorder, history of mania)
- Suspicion or history of substance abuse
- Clinician discomfort with the case
- Medication advice (psychiatrist or other mental health prescriber)
- Patient request for more specialized treatment

Integrate Measurements into Monitoring and Follow-Up

Measurement-based care refers to the systematic use of measurement tools, such as validated rating scales, to monitor the trajectory of disease course and treatment response and support clinical decision-making. Using simple rating scales for measurement-based care of depression can improve outcomes such as symptom remission and adherence [62]. Many of the same instruments previously mentioned in this course can be used for this purpose. Among the most widely used instruments are the Inventory of Depressive Symptoms (IDS), the HAM-D, the MADRS, the PHQ-9, and the BDI [22].

Routine monitoring of patient outcomes should go beyond assessing depression symptoms by including the ongoing evaluation of functional impairment and quality of life. These outcomes are more important and relevant to patients, and each may vary independently of symptoms. Assessing functionality should include evaluating social and occupational/educational functioning. Quality-of-life assessments offer the opportunity to more broadly evaluate patient well-being and overall health satisfaction [62]. The use of measurement tools should supplement and not replace clinician judgment [206; 207].

HERBAL MEDICATIONS, DIETARY SUPPLEMENTS, AND ALTERNATIVE THERAPIES

Up to 50% of patients with depression use complementary therapies [208]. Herbal medications, dietary supplements, and alternative therapies for depression are appealing to many patients because they are perceived as being natural, helpful, and free of the potentially troubling side effects associated with pharmaceutical antidepressant treatment. Patients ambivalent about taking psychiatric medication are also likely to gravitate to these therapy approaches [209].

All patients should be asked if they are taking over-the-counter dietary supplements or herbal medications, to avoid adverse drug-drug interactions. Because many patients use complementary/alternative therapies, clinicians should have a clear understanding of the most common modalities and potential impact on treatment course and outcomes.

Acupuncture

Acupuncture treatment of depression has shown mixed results, with some randomized controlled trials showing a significant treatment effect and others showing no significant difference from controls. Acupuncture may be an option for those who reject conventional treatments, for patients with milder depression, or for pregnant or nursing women for whom the risks of pharmacotherapy are greater [21].

S-adenosylethionine (SAMe or Sam-E)

S-adenosylethionine (SAMe) is a naturally occurring compound that is present in most parts of the human body and is involved in immune processes and the metabolism of dopamine, serotonin, and melatonin. Several studies have found that compared with placebo, SAMe is efficacious in oral doses of 800–1,600 mg/day, with side effects that were mild and transient. Overall, parenteral and oral formulations of SAMe are comparable to TCAs in efficacy in the treatment of MDD and are better tolerated. SAMe may also have comparable efficacy to TCAs in subgroups such as postpartum women and patients with HIV [22].

Hypericum perforatum (St. John's Wort)

St. John's wort possesses an SSRI-like mechanism, and although considered a first-line antidepressant in many European countries for mild-to-moderate depression, there is no consensus on its efficacy in MDD. Overall, the data suggest that St. John's wort has efficacy comparable to low-dose TCAs in mild-to-moderate depression but is better tolerated by patients. However, St. John's wort interacts with many drugs, including other antidepressants, warfarin, oral contraceptives, and antiretroviral, anticancer, and antirejection drugs. With numerous potential drug interactions, St. John's wort cannot be considered a benign agent, and further studies are needed [175; 210; 211; 212; 213; 214; 215].

Inositol

Myo-inositol is a glucose isomer and an essential component of the phosphatidylinositol second messenger system, which is critically linked to several CNS receptor signaling systems [216; 217; 218; 219]. Randomized controlled trials have found inositol treatment superior in efficacy to placebo in the treatment of major depression, panic disorder, and obsessive-compulsive disorder, and equivalent to fluvoxamine 150 mg/day in panic disorder [216; 220; 221; 222]. The effective daily dose is 12–18 grams, and inositol at 18 g/day is free of side effects other than loose stools and drowsiness [223]. These results need replication in larger trials but are intriguing. A 2010 study demonstrated that patients with severe depression receiving repetitive transcranial magnetic stimulation therapy showed significantly elevated myo-inositol levels in the left prefrontal cortex; greater elevation correlated with more robust clinical improvement [224]. A small meta-analysis published in 2014 suggests that inositol may be particularly beneficial for patients with premenstrual dysphoric disorder [225]. Myo-inositol is available in nutritional supplement stores but is largely unknown as an antidepressant and anxiolytic in the United States.

Folate

The use of folate in non-folate-deficient patients with MDD may be most effective as augmentation to SSRIs such as fluoxetine. Persons receiving fluoxetine and folate may have fewer side effects from the SSRI than those receiving fluoxetine alone [22].

Saffron (*Crocus sativus L.*)

Saffron is a spice that has been used for the treatment of depression in Persian traditional medicine. Its proposed mechanism involves serotonergic, antioxidant, and anti-inflammatory effects [226]. Several well-designed clinical trials have evaluated the efficacy of saffron 30 mg daily over six to eight weeks in mild-to-moderate depression. The results suggest saffron may be more effective than placebo, at least comparable in efficacy to therapeutic-dose imipramine and fluoxetine in reducing depressive symptoms, and without significant side effects. However, this evidence should ideally be replicated in Western populations [227; 228; 229; 230; 231].

Omega-3 Fatty Acids

Evidence suggests omega-3 fatty acids may be beneficial in mood disorders. Treatment efficacy in MDD cannot be determined, but subgroups such as children and pregnant women may show meaningful clinical response. Side effects are minimal [22].

Sleep Deprivation

Sleep deprivation therapy involves staying awake through one night and the following day, without any sleep. Although the proposed antidepressant mechanism is poorly understood, clinical trials have consistently shown that around 60% of depressed persons experience moderate improvement to total remission. However, relapse occurs in 50% to 80% of responders within several days of treatment. Persons with mild depression usually experience a worsening of symptoms [209]. A 2022 systematic review and meta-analysis found no evidence of benefit for sleep deprivation therapy in reducing depressive symptoms [232].

Bright-Light Therapy

Bright-light therapy is effective in patients with MDD with season variation (i.e., seasonal affective disorder) and may also be efficacious as monotherapy treatment of MDD without season variation. The correct intensity of light is essential and should be 3,000 to 10,000 lux-hours of white light, administered at least 30 minutes per day [22]. Results of a systematic review suggest that bright-light therapy at 5,000 lux or greater for periods of 30 minutes or more may be useful as an augmentation to standard antidepressant pharmacotherapy for treatment of MDD [233].

Botulinum Toxin A Injection

Botulinum toxin A injection is emerging as a novel, effective treatment for MDD. It is widely used in aesthetic medicine to treat glabellar frown lines and has been introduced in the treatment of headaches, muscle pain, and tremor. Patient reports of diminished irritable, depressed, and anxious mood following injection led to its evaluation as treatment of MDD. The first trial of botulinum toxin A (29 units in women, 39–40 units in men) in moderate-to-severe chronic MDD found remission in eight of nine subjects after a single injection in the glabellar region [234]. Functional MRI of patients with MDD shows diminished amygdala responses to negative stimuli after injection of botulinum toxin A, confirming that afferent feedback from the corrugator muscle to the amygdala is reversibly severed [235].

In pooled results from three subsequent randomized controlled trials, single-treatment botulinum toxin A led to significantly greater reductions in mean depression scores (47% vs. 16%), response (52% vs. 8%), and remission (42% vs. 8%) rates than placebo. Age, sex, depression severity, and current antidepressant use were not significantly related to response [235]. One small trial found greater response in patients with higher anxious or agitation levels [236]. Symptom reduction is noted around two weeks post-injection and efficacy wears off by three to six months; maintenance injections every three months can be used for relapse prevention. A study from 2021 found that the efficacy of botulinum toxin A was comparable with the antidepressant sertraline for treatment of depression [237]. Use of botulinum toxin A for MDD is currently in phase 3 clinical trials and is off-label [238].

EVIDENCE-BASED INTERVENTIONS TO IMPROVE PATIENT ADHERENCE TO ANTIDEPRESSANT MEDICATION	
Intervention	**Overview**
Patient education	Inform patient of the causes and course of depression, and the effects, duration, and side effects of treatment.
Patient-provider empathy/alliance	Establish a good relationship between patient and provider, with an emphasis on communication, consensus, and understanding.
Clinical management strategies	Provide advice regarding a standardized approach to taking medications and compliance, and allow for frequent follow-up visits, especially during initial phases of treatment.
Simplicity of treatment	Minimize the number and doses per day of medication.
Active management of side effects	Inform patient about side effects, monitor their occurrence, provide reassurance, and adjust the treatment if needed.
Behavioral feedback	Help patients incorporate treatment into daily routine (e.g., modify schedule to fit medication routine, behavioral reminders, pill boxes, easy-to-read prescription labels).
Preference for SSRIs	When possible, use SSRIs due to greater tolerability relative to TCAs.
Physician training	Improve skills on caring for patients with depression and patient adherence to treatment.
Source: [242]	*Table 4*

STRATEGIES FOR INADEQUATE RESPONSE TO INITIAL THERAPY

If a patient fails to adequately respond to an initial antidepressant and/or psychotherapy trial, the clinician should consider adjusting the treatment plan, re-evaluating the initial diagnosis, and/or optimizing the prescribed therapy. If the patient remains unresponsive to treatment, referral to a psychiatrist may be indicated.

Optimize Treatment

Optimizing treatment helps to ensure the patient is receiving the most potential benefit from their initial antidepressant. This involves optimizing the dosage and adherence to treatment.

Increase the Dose of the Initial Antidepressant

There is substantial evidence that many patients receive subtherapeutic doses. When the antidepressant is tolerable but partial or no response is shown by three to four weeks, increase the dose by increments to the highest recommended dose [64]. SSRI dose escalation is supported by a 2016 meta-analysis that found greater response in high-dose ranges, with a plateau at doses greater than 250 mg imipramine-equivalent. This benefit is somewhat offset by decreased high-dose tolerability [239].

Enhance Treatment Adherence

Patient nonadherence can result in nonresponse to the optimal antidepressant regimen, and intolerance of side effects strongly influences therapy nonadherence [240]. Poor adherence is a major problem for patients receiving antidepressant treatment, with discontinuation rates ranging from roughly 30% in clinical trial settings to as high as 60% in clinical practice [241; 242]. In an evaluation of patient adherence to antidepressant medications, 28% had discontinued treatment within the first month and 51.2% had stopped their antidepressant medication by the fourth month [243]. At all timepoints, roughly 64% of patients cited side effects as the reason for stopping their medication.

Compared with usual care, support programs (i.e., a collaborative care model) that educate patients on the value of medication adherence and the potential side effects of antidepressants and provide follow-up to ensure continued compliance have been found to improve the efficacy of depression treatment (***Table 4***) [244; 245]. Other research has shown that patients receiving five specific instructions were significantly more likely to continue their medication through the first month of therapy [64; 243]:

- Take the antidepressant daily.
- Antidepressants must be taken for at least two to four weeks to see a noticeable effect.
- Continue to take the antidepressant even if you feel better.
- Do not stop taking antidepressants without checking with your healthcare provider.
- Follow instructions to contact your healthcare provider when questions arise about antidepressants.

Interventions to improve medication adherence have been found to be effective for up to six months, but the evidence for long-term effectiveness is insufficient and further research is needed [246].

Re-Evaluate the Diagnosis

Most patients with MDD have comorbid conditions that can contribute to disease burden and interfere with treatment response [247]. Especially when undiagnosed, MDD with highly anxious features, comorbid panic disorder, social anxiety disorder, or obsessive-compulsive disorder is strongly predictive of poor medication response, side effect intolerance, treatment discontinuation, and worse overall prognosis. Alcohol or substance use disorder contributes to poor treatment response; in these cases, involve addiction specialists as needed [241]. A behavioral health provider should be involved if a personality disorder is present [248]. Patients with bipolar disorder may require a different treatment approach, and hypomanic, mixed, or manic histories may not be apparent during the initial evaluation [21].

Patients with chronic subtypes of depression (i.e., chronic MDD, double depression, recurrent MDD) may take longer to respond to treatment; clinicians or patients may assume non-response and prematurely discontinue treatment. Different depression subtypes may respond preferentially to various antidepressants [249].

Adjust the Treatment

Options for patients lacking benefit from their initial antidepressant include switching antidepressants, switching to or adding psychotherapy, and adjunctive strategies (i.e., adding a second medication). The decisions to switch or add medications should be individualized and based on clinical factors [158]. Clinicians may consider switching to another antidepressant when [158]:

- It is the first antidepressant trial.
- Side effects are poorly tolerated.
- Minimal or no response (i.e., <25% improvement).
- There is more time to wait for a response (e.g., less severe, less functional impairment).
- Patient prefers switching to another antidepressant.

An adjunctive medication may be added when [158]:

- There have been two or more antidepressant trials.
- The initial antidepressant is well tolerated.
- There is partial response (i.e., >25% improvement).
- There are specific residual symptoms or side effects to the initial antidepressant that can be targeted.
- There is less time to wait for a response (e.g., more severe, more functional impairment).
- Patient prefers to add on another medication.

Switch to Another Antidepressant

Lack of response to one first-line antidepressant does not preclude potential benefits from other antidepressants, but the value of switching between classes or within classes of antidepressants is debatable. Switching to an antidepressant with evidence of superior efficacy is recommended over switching to a lower-efficacy antidepressant based on it being in a different class [158]. Among switching strategies for poor initial SSRI response or tolerance, switching to venlafaxine seems most effective [110].

Combining or Switching Antidepressants and Psychotherapy

Switching from an antidepressant to psychotherapy or vice versa appears useful for non-responders to initial treatment [250]. The addition of CBT or another medication can result in similar rates of improvement, although the addition of medication may result in a more rapid response [251].

Psychotherapy may provide better outcomes on adjustment and functional measures such as mood, suicidal ideation, work, and interests. Medication treatment may be superior on vegetative symptoms such as sleep [252].

Improvement with initial treatment with psychotherapy is typically slower than with pharmacotherapy. A decision regarding progress with psychotherapy and the need to change or augment this treatment modality may require 8 to 10 weeks before evaluation [21; 253]. If a patient has received psychotherapy and not responded, evaluate the treatment and consider another type.

Augmentation

Patients with MDD often prefer augmentation (add-on) to switching if partial improvement is achieved with the initial agent [254]. Standard antidepressants are frequently used as add-on therapy to enhance efficacy. For example, combining a TCA and an SSRI may be helpful for some patients, but the TCA dose should be adjusted because SSRIs may increase TCA levels [255; 256]. Combining an SSRI, SNRI, or TCA with a presynaptic a2-autoreceptor antagonist (e.g., mirtazapine, trazodone) has shown significantly greater benefit than other combinations, with dosage differences accounting for about 50% of the total difference in treatment effect. Tolerability, as measured in patient dropout, was lower than expected with this combination [257].

Adverse effects are higher in combination pharmacotherapy, and combining antidepressants at treatment initiation is not recommended unless the MDD is characterized as severe (i.e., PHQ-0 >20); chronic (duration longer than two years); and recurrent (three or more episodes) [64]. In patients lacking response to their initial or switched standard antidepressant, evidence indicates that standard monoamine antidepressants are not sufficient for many patients and other mechanistic targets are needed [150].

Aripiprazole has been found superior to switching antidepressants in patients with current depressive episodes, despite adequate antidepressant dosage, and in patients with antidepressant non-response [258]. Brexpiprazole is another atypical antipsychotic effective as add-on therapy; aripiprazole and brexpiprazole are approved by the FDA as augmentation therapies in MDD [64; 150; 192]. Although well tolerated, brexpiprazole does not appear to offer a statistically significant benefit over placebo as an adjunctive treatment [259].

The evidence base for lithium and triiodothyronine shows efficacy, but mainly involves studies that combined these agents with TCAs or MAOIs [150]. Methylphenidate has mostly shown mixed results in reducing depressive symptoms [260; 261].

Modafinil has not shown consistent efficacy in core MDD symptoms, but it has demonstrated improvements in symptoms/dimensions of psychopathology highly relevant to patient function, including fatigue, apathy, anhedonia, amotivation, and cognitive impairment [262]. Adverse effects have not differed from placebo [159; 263].

Lisdexamfetamine, a dextroamphetamine prodrug, showed some evidence of efficacy as an adjunctive agent for partial SSRI responders in two placebo-controlled randomized controlled trials [182; 264]. Pramipexole is a dopamine receptor agonist and a standard therapeutic in Parkinson disease. Preliminary evidence shows some benefit in patients with MDD lacking response to multiple antidepressant regimens [265; 266].

The optimal duration of add-on therapy is not known, but it seems prudent that patients who are tolerating treatment and achieving therapeutic objectives should continue for at least 6 to 12 months with ongoing reassessment, with indefinite continuation for many [150].

TREATMENT-RESISTANT DEPRESSION

Most definitions of treatment response compare changes in depression rating scale scores between pre-treatment and follow-up. Standardized rating scales such as the MADRS and HAM-D are widely used to quantify treatment response [249]. As discussed, the definition of antidepressant response falls into four categories [21; 111]:

- Remission: The absence of depressive symptoms or minimal symptoms (HAM-D score ≤7)
- Response: A 50% or greater reduction in symptoms
- Partial response: A 25% to 50% reduction in symptoms
- Nonresponse: The absence of meaningful response (symptom reduction ≤25%)

Standard antidepressants fail to produce adequate response in 30% to 50% and remission in up to 70% of patients with MDD [267; 268; 269]. Partial response, instead of full remission, leaves patients with impairing residual symptoms and high risk of relapse. Each relapse increases symptom severity, decreases treatment response, and heightens risk of treatment-resistant MDD [270].

Treatment-resistant depression is a problem increasingly encountered by primary care and mental health providers. Contributors to treatment-resistant depression include illness severity, medical and psychiatric comorbidity, and the limitations of FDA-approved drug options. The definition of treatment resistance lacks consensus, but the most common definition is inadequate response to two or more antidepressants. This does not consider adjunctive strategies or distinguish patients with partial versus non-response [158; 180].

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

OPTIONS FOR TREATMENT-RESISTANT DEPRESSION

Bright-Light Therapy

As mentioned, use of bright-light therapy for treatment of major depression with a seasonal specifier (seasonal affective disorder) is well established [271; 272]. There is also evidence supporting its use for additional types of depressive symptom patterns, including non-seasonal depression, milder variations of seasonal depressive patterns, and depression in pregnant and postpartum women [273; 274; 275]. Bright-light therapy may quicken and enhance the effects of antidepressants [276]. The interaction between light intensity and duration of exposure requires two hours daily with 2,500 lux, one hour with 5,000 lux, and 30 minutes daily with 10,000 lux for efficacy [277]. Light therapy must also use equipment that eliminates ultraviolet frequencies.

Neurostimulation Therapies

The limitations of standard antidepressants, frequent treatment resistance, and the paradigm shift in psychiatry away from specific neurotransmitter focus and toward an integrative neural network perspective has prompted the development of novel depression treatment approaches, such as neurostimulation therapy. Neurostimulation therapies include a range of techniques that deliver electrical or magnetic stimulation to specific brain region targets for the treatment of refractory psychiatric and pain conditions. Neurostimulation efficacy in neurologic disorders led to their introduction in psychiatry. In addition to ECT, several others are now FDA-approved for use in MDD and related disorders.

The dorsolateral prefrontal cortex is a common brain stimulation target in patients with MDD. Its normal regulatory function of control over stress and emotion reactivity is thought to be hypoactive in MDD. The dorsolateral prefrontal cortex and rostral anterior cingulate cortex areas are closely interconnected; decreased activity in these frontal areas accounts for apathy, psychomotor slowness, and impaired executive functioning common in patients with MDD [278; 279; 280].

Electroconvulsive Therapy

ECT remains established as a potent and rapidly acting treatment for severe or refractory MDD and is considered unrivaled among standard options for rapidly inducing antidepressant effects. ECT is effective as acute treatment, but multiple treatments are required and many who respond experience symptoms again within six months [281]. ECT generates electrical stimuli for seizure induction through electrodes applied to the scalp, with the patient under general anesthesia and premedicated with a muscle relaxant. Clinical outcomes are highly influenced by electrode placements, electrical intensity, and pulse width [282]. Seizure-induced changes in neurotransmitter activity, neuroplasticity, and functional connectivity account for its effects. ECT also increases brain-derived neurotrophic factor, which may promote neuroplasticity and contribute to the antidepressant effect [282; 283].

As first-line treatment, ECT is used for severe melancholic, catatonic, psychotic, or refractory depression and for patients who refuse to eat or drink, have very high suicide risk or severe distress, pregnant women with severe depression, or who have a previous positive ECT response [64; 281; 284]. A large study reported 95% remission in study completers [285].

Full ECT response requires at least four to six sessions delivered two to three times per week. Twice weekly ECT requires longer treatment duration, but more than three treatments per week is not recommended due to the greater cognitive side effect risk [282]. Relapse rates are greatest in the first six months post-ECT (37.7%). Even patients with maintenance ECT show high relapse rates at one year (51.1%) [286]. Severity of treatment resistance predicts poor ECT response [287; 288].

Adverse Effects

Headaches (45%), muscle soreness (20%), and nausea (1% to 25%) during ECT are transient and treated symptomatically; 7% of patients with MDD switch into a manic or mixed state [282]. Cognitive impairment includes transient post-ECT disorientation, retrograde amnesia (i.e., difficulty recalling information learned pre-ECT), and anterograde amnesia (i.e., difficulty retaining information learned post-ECT). Mild, short-term memory and cognitive impairments are common during, and just after, ECT [284]. Within two to four weeks, impaired anterograde memory usually returns to normal or may improve from pre-ECT levels [289]. Retrograde impairment can persist for prolonged periods [290]. Most distressing to some patients is loss of autobiographic memory recall, infrequently reported to persist beyond six months [284]. ECT lacks absolute contraindication, but increased safety risk is associated with space-occupying cerebral lesion, increased intracranial pressure, recent cerebral hemorrhage, or aneurysm [282; 283].

Vagus Nerve Stimulation

Vagus nerve stimulation uses an implantable device to provide intermittent stimulation to the left vagus nerve (80% afferent to the CNS) [21]. It received FDA approval for treatment-resistant depression in 2005 due to the lack of approved drug treatments and concerns over the long-term efficacy and safety of ECT [291].

Controlled studies with follow-up six months or longer have found significant improvements in depressive symptoms that were often sustained over time, with relapse rates relatively low [292]. Long-term vagus nerve stimulation can lead to significant side effects, including decreases in airway flow and respiratory effort and laryngopharyngeal dysfunction [293]. Given the profound negative impact of treatment-resistant depression and lack of durable response in some patients, vagus nerve stimulation may be a useful option [294]. In a 2017 trial, patients with treatment-resistant MDD and four or more failed depression treatments (including ECT) received vagus nerve stimulation or treatment as usual and were followed five years. Response was a ≥50% decrease in MADRS score at any follow-up visit. Subjects who received vagus nerve stimulation (compared with usual treatment) had more severe treatment-resistant depression on several dimensions [295]. Vagus nerve stimulation led to greater five-year cumulative response (67.6%) and remission (43.3%) rates compared with usual treatment (40.9% and 25.7%, respectively). However, vagus nerve stimulation response often required 12 or more months to appear [295]. Guidelines recommend against the use of vagus nerve stimulation outside a research setting [64].

Deep Brain Stimulation

With deep brain stimulation, an electrode is surgically implanted to stimulate the subgenual cingulate gyrus with high-frequency impulses to reduce depressive symptoms [21]. Deep brain stimulation is invasive and carries the risk of infection, hemorrhage, and other surgical complications. Stimulation-induced adverse effects such as facial contractions, facial paresthesias, olfactory phenomena, anxiety, and mood fluctuations have been reported, particularly at higher levels of stimulation [296].

Most clinical improvement shows delayed onset; one trial in patients with treatment-resistant depression reported remission rates of 27%, 24%, and 37% at three-month, six-month, and two-year follow-up, respectively [297]. Deep brain stimulation can increase the risk of suicide ideation, attempts, and death, strongly indicating that patients should be pre-screened for suicide risk and monitored closely for suicidal behavior pre- and postoperatively [298]. Deep brain stimulation is investigational for treatment-resistant depression and is reserved for use in patients with severe refractory psychiatric, neurologic, or chronic pain conditions [282; 296].

Transcranial Magnetic Stimulation

Repetitive transcranial magnetic stimulation delivers high-intensity magnetic pulses to the cortex through a stimulating coil placed to the forehead [299; 300]. It is a first-line MDD treatment in patients with one or more failed antidepressant trial [282]. Efficacy in treatment-resistant depression was established using stringent criteria; analysis of 23 trials found significantly greater efficacy and effect size for repetitive transcranial magnetic stimulation over sham [301]. In randomized clinical trials, 20 to 30 sessions over four or more weeks achieved 40% to 55% response and 25% to 35% remission rates [302].

The most frequent side effects are transient scalp pain (40%) and headache (30%). Both diminish with repeated treatment and respond to over-the-counter analgesics. The cognitive safety profile is benign. Seizures are the most serious side effect, but fewer than 25 cases have been reported worldwide [282; 303]. Repetitive transcranial magnetic stimulation is contraindicated in patients with any metal or metallic hardware in the head (except the mouth), with a history of seizures, and who take medications that lower seizure threshold [282; 304].

Transcranial Direct-Current Stimulation

A sham-controlled trial randomized patients with MDD to escitalopram (20 mg/day) or prefrontal transcranial direct-current stimulation for 10 weeks. With mean decrease in HAM-D score from baseline, both treatment groups were superior to placebo, but transcranial direct-current stimulation was inferior to escitalopram. New-onset manic switch during transcranial direct-current stimulation therapy is a concerning adverse event; however, the number of reported cases is low [283; 305; 306].

Magnetic Seizure Therapy

Magnetic seizure therapy uses focused brain stimulation (generally of the right frontal area) to induce a focal seizure. It intends to produce the efficacy of ECT without the cognitive side effects by sparing the hippocampus from seizure activity [21]. A meta-analysis of 1,092 patients with treatment-resistant depression found response and remission rates for active vs. sham magnetic seizure therapy of 25% and 17%, versus 9% and 6%, respectively [307]. A 2016 meta-analysis found that while magnetic seizure therapy had a small short-term effect in improving depression compared with sham, follow-up studies did not demonstrate that the small effect would continue for longer periods [308]. A study of 23 patients with treatment-resistant depression found that 44.4% of the group experienced resolution of suicidal ideation following magnetic seizure therapy [309]. Magnetic seizure therapy add-on to SSRI treatment in treatment-resistant depression improves outcome, but more data is needed before it can be considered a first-line therapy for treatment-resistant depression [307; 310].

Pharmacotherapies

Ketamine

Ketamine is an *N*-methyl-D-aspartate receptor (NMDA-R) antagonist that was approved for use as an anesthetic in 1970. Demonstration that a single IV dose in patients with treatment-resistant depression reliably produced rapid, robust antidepressant effects for one week was a breakthrough discovery for research and a turning point for patients for whom all other treatment approaches had failed [311]. The short-term efficacy of ketamine treatment of refractory MDD and bipolar depression is now established; over a dozen placebo-controlled trials have shown that patients with refractory MDD or bipolar depression have significantly greater response, remission, and depressive symptom reduction to single-dose IV ketamine than placebo from 40 minutes through days 10 to 12 post-treatment [312; 313]. The approach has become standardized, using a sub-anesthetic dose: 0.5 mg/kg IV over a 40-minute infusion. In a 2015 analysis, ketamine was designated as one of two psychiatric treatments that had the highest potential impact on patient outcomes. This designation was based on the serious unmet need for fast-acting, well-tolerated antidepressants with efficacy in refractory MDD and bipolar depression [47].

Substantial interest and optimism among patients, families, patient advocacy groups, and clinicians has been generated by clinical reports of unique antidepressant effects with ketamine and frequent media coverage of potential ketamine treatment benefits. Demand for clinical access to ketamine treatment is rapidly escalating, and a growing number of clinics and practitioners are now offering various forms of ketamine treatment for mood and anxiety disorders throughout the United States [314]. However, many in the field suggest greater caution, and concerns that enthusiasm and desperation of patients and families may be leading to ketamine used in ways that are not yet supported by existing evidence. Others note the lack of large-scale or long-term studies of ketamine treatment in refractory MDD [314]. Use of IV ketamine for treatment-resistant depression is off-label, whereas an intranasal formulation (esketamine) is FDA-approved for treatment-resistant depression and for MDD with suicidality, when used in conjunction with an oral antidepressant [64; 175]. A systematic review and meta-analysis of five randomized controlled trials found that twice-weekly dosing of esketamine as augmentation to ongoing oral antidepressant use compared with placebo improved depressive symptoms and remission in patients with MDD at up to 28 days follow-up [315].

Rapastinel

Rapastinel is an investigational NMDA-R partial agonist with robust cognitive enhancement and rapid, long-lasting antidepressant effects. This drug comes as a pre-filled IV syringe, administered in less than one minute. After one injection, therapeutic effects appear within two hours and last up to seven days. Rapastinel is well-tolerated, and antidepressant effects last up to 10 weeks with repeat dosing. The drug has

no psychotomimetic effects, may be neuroprotective, and may enhance aspects of learning and memory. The long-lasting therapeutic benefits are explained by significant effects on metaplasticity processes in the medial prefrontal cortex and hippocampus [316; 317].

Buprenorphine

Opioids were widely used as depression treatment from roughly 1850 until 1956, when they were replaced by standard antidepressants. Their antidepressant potential has rarely been studied in the past 60 years, but this seems to be changing. The synthetic opioid buprenorphine is a partial mu opioid receptor agonist and kappa opioid receptor antagonist. It is safer in overdose with substantially less euphoria than traditional opioid analgesics such as morphine and oxycodone. A small, open-label study in 1995 hinted that buprenorphine might have benefit in refractory depression [318].

Buprenorphine/samidorphan combination (BUP/SAM) is an opioid system modulator being investigated as an adjunctive treatment for MDD. It is a fixed-dose combination of buprenorphine and samidorphan (a mu opioid receptor agonist). Samidorphan was added to address the abuse and dependence potential of buprenorphine [319]. A 2019 long-term open-label extension study examined the efficacy and adverse effects of adjunctive BUP/SAM [320]. All patients had confirmed MDD and a current MDE lasting 2 to 24 months. Patients were treated with an established antidepressant therapy for a minimum of 8 weeks before receiving sublingual BUP/SAM (2 mg/2 mg) for up to 52 weeks. Safety was assessed via reported adverse events, the Columbia-Suicide Severity Rating Scale, and the Clinical Opiate Withdrawal Scale. Evaluation of efficacy was achieved using MADRS. Of 1,485 patients, 50% completed the study; 11% withdrew due to adverse events (e.g., nausea, headache, constipation, dizziness, somnolence). Drug withdrawal adverse events were infrequent, and euphoria-related adverse events were uncommon. There was no evidence of increased suicidal ideation or behavior. Improvements in MADRS scores were maintained until the end of the study, suggesting durability of antidepressant effect. BUP/SAM was generally well tolerated, with a low risk of abuse [320].

Celecoxib

The cyclooxygenase-2 inhibitor celecoxib has demonstrated significant reductions in depressive symptoms compared to placebo as an SSRI add-on in MDD treatment. The decrease in depressive symptoms begins after the first week. However, celecoxib and all other nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with risk of serious cardiovascular events [321].

Statins

Two studies compared statins to placebo as add-on therapy to fluoxetine in the treatment of MDD. In one trial, 30 mg/day lovastatin for six weeks improved antidepressant effects compared to placebo [322]. The other trial found simvastatin 20 mg/day for six weeks significantly decreased depressive symptoms, but remission did not differ from placebo [323].

Statins have relatively few side effects; the most dangerous—rhabdomyolysis—is a very rare event. Statins are primarily used in prevention of cardiovascular events but may have a more favorable benefit/risk balance than other drugs, such as NSAIDs, considering the high cardiovascular comorbidity in persons with depression [324]. Other less common side effects include myopathy, hepatotoxicity, peripheral neuropathy, impaired myocardial contractility, and autoimmune dysfunction.

Silexan

Silexan is a substance derived from Lavandula angustifolia flowers that increases extracellular serotonin levels. Approved in Germany for the treatment of restlessness related to anxious mood, its antidepressant effects were tested in a randomized controlled trial of 318 patients with mixed anxiety and depressive disorder. Silexan (vs. placebo) significantly reduced MADRS and Hamilton Rating Scale for Anxiety (HAM-A) scores. Antidepressant effects were noted after 2 weeks, became statistically significant at 4 weeks, and remained significant through the 10-week trial [123; 321].

Psilocybin

Psilocybin is a classical psychedelic and naturally occurring alkaloid found in the *Psilocybe* genus of mushrooms [325]. Its potential efficacy in the treatment of depression is a recent focus of research interest.

The feasibility, safety, and efficacy of open-label psilocybin were studied in 12 patients with treatment-resistant depression (2 to 13 failed antidepressant trials). All patients received 10-mg (low-dose) oral psilocybin, 25-mg (high-dose) psilocybin one week later, and psychologic support during all sessions. Relative to baseline, depressive symptoms were markedly reduced one week and three months after high-dose treatment. Remission was achieved by 67% at one week and 42% at three months. Marked and sustained improvements in anxiety and anhedonia were also noted. Psilocybin was well tolerated by all patients, without serious or unexpected adverse events [325].

Two psilocybin treatment studies in patients with life-threatening cancer and high levels of depressive and anxious distress were published in 2016. One trial compared low-dose psilocybin (0.3 mg/kg) with niacin placebo, and the other trial compared low-dose (1 or 3 mg/70 kg) and high-dose (22 or 30 mg/70 kg) psilocybin [326; 327]. Patients in all sessions were accompanied by trained therapy support. Both studies reported significant improvements in depression and anxiety scores, measures of spiritual well-being, emotional distress related to the cancer, and quality of life. Immediate post-treatment gains were sustained for six-month study durations by 60% to 80% of subjects. These studies confirmed psilocybin could be given safely without significant adverse effects in a controlled environment with trained therapists [326; 327].

FDA RATINGS OF ANTIDEPRESSANT PREGNANCY RISK	
Rating	**Definition and Examples**
A	No currently available antidepressant medications are rated A, which would indicate a failure to demonstrate risk to the fetus in well-controlled studies of pregnant women.
B	Maprotiline—no evidence of risk in humans, and either animal findings show risk but human findings do not, or animal findings are negative if no adequate human studies have been performed.
C	Amitriptyline, amoxapine, bupropion, protriptyline, sertraline, trazodone, trimipramine, and venlafaxine—risk cannot be ruled out, and although human studies are lacking and animal studies are either positive for fetal risk or are lacking, potential benefits may justify the potential risks.
D	Imipramine, nortriptyline, and paroxetine—positive evidence of risk. Investigational or postmarketing data show risk to the fetus. The potential benefits may outweigh the potential risks, and if needed in a life-threatening situation or a serious disease, the drug may be acceptable if safer drugs cannot be used or are ineffective.
X	No currently used antidepressant medications are rated X, which would indicate that use is contraindicated in pregnancy due to animal or human studies that conclude that fetal risk clearly outweighs potential benefits.
Source: [21]	*Table 5*

PERINATAL DEPRESSION

Approximately 5% to 14% of women experience significant mood or anxiety symptoms during pregnancy, and the goal of perinatal treatment is to minimize the risks of both depression and its treatment to the mother and child [328; 329]. Misperception about treatment risk can result in the termination of otherwise wanted pregnancies or avoidance of needed pharmacotherapy. By informing patients of both the nature of medication risks and the risks of untreated illness, providers can help patients reach their own educated decisions.

For depressed pregnant women, both continuous SSRI exposure and continuous untreated depression are associated with preterm birth rates in excess of 20% [330]. The potential impact of untreated maternal depression on pregnancy outcome and infant health include preterm birth and low birth weight, birth defects, developmental delay and cognitive impairment, behavioral and emotional maladjustment, and poor maternal health behaviors such as smoking and alcohol and substance use, which secondarily affect birth outcome [331].

MILD-TO-MODERATE DEPRESSION

Several non-drug therapies effective in mild-to-moderate depression are available for pregnant and breastfeeding women, including interpersonal psychotherapy, bright-light therapy, and CBT [332; 333; 334]. Interpersonal therapy is efficacious in postpartum depression and can improve functioning for six months postpartum [334]. While these interventions are more efficacious than routine care for postpartum depression, there is little indication of superiority for any one intervention [334]. Other nonpharmacologic treatments that may be effective include acupuncture, progressive relaxation, music therapy, sleep deprivation, and exercise [331]. Empirical support for nutritional or supplemental omega-3 fatty acids is lacking, although they pose little to no risk of adverse effects [335]. Progesterone is ineffective in postpartum depression and may intensify depressive symptoms in some patients [331].

SEVERE DEPRESSION

In many circumstances, the risks of untreated illness may outweigh the potential negative effects of certain antidepressant medications. Partial SSRI treatment during pregnancy to reduce the risk of preterm birth is not recommended, as inadequate dosing does not successfully treat the depression. When possible, medication choice should be based on what has worked previously and the risk/benefit of continuing the current medication during pregnancy and/or postpartum. Optimal dosing and safety is best ensured by consultation with a health professional with perinatal expertise.

PHARMACOLOGY AND PERINATAL DEPRESSION

The largest amount of reproductive safety information is available for TCAs and SSRIs (***Table 5***). Available pregnancy data have found no evidence that fluoxetine, sertraline, fluvoxamine, venlafaxine, or bupropion are associated with an increased risk of major congenital malformations. In 2006, the FDA warned that paroxetine was associated with increased risk for cardiovascular malformations compared to other antidepressants. Therefore, women of childbearing age taking paroxetine should be advised of the potential risk, and other treatment options should be considered [175; 336].

The use of SSRIs before the 20th week of gestation has not been associated with persistent pulmonary hypertension, but use of SSRIs in late pregnancy has shown a small but significantly increased risk of persistent pulmonary hypertension [337; 338]. Several case reports document a perinatal syndrome in infants (e.g., jitteriness, irritability, bowel obstruction, urinary retention) with maternal use of TCAs and most of the SSRIs, although it is unclear whether the neonates were

exhibiting symptoms of SSRI toxicity or SSRI withdrawal at birth. Also, they may have been more irritable and difficult to settle due to maternal depression, anxiety, and exposure to psychological stressors [328; 339; 340; 341; 342]. There is a lack of evidence suggesting that reducing or discontinuing antidepressants in late pregnancy will reduce adverse neonatal effects [343].

Women with a history of depression who are planning to become pregnant should carefully consider the choice and timing of an antidepressant [340]. Although SSRIs taken during pregnancy may be associated with adverse neonatal effects that are mostly mild and short-lived, women with a history of recurrent or severe depression who discontinue antidepressants during pregnancy increase the risk of potentially adverse outcomes for both the mother and fetus/infant. The minimum effective antidepressant dose to achieve and maintain remission should be used throughout pregnancy in women who continue their medication, and these patients should be monitored on an ongoing basis [339]. Women who discontinue medication relapse significantly more frequently over the course of their pregnancy compared with women who maintain their medication [344]. The decision to continue treatment during the pregnancy should balance the risks and benefits to the mother and child and should be made on a case-by-case basis [21].

LACTATION

The Academy of Breastfeeding Medicine Protocol Committee suggests that TCAs and SSRIs are relatively safe, but they should only be used when clearly needed. Assessments weighing the potential benefits with the potential risks to the nursing infant should be performed in all cases [345]. Also, the mother-infant pair should be monitored for the emergence of adverse effects or complications [345; 346]. Regarding the use of specific medications during lactation, several observations and recommendations have been made [21; 347; 348]. Sertraline, paroxetine, nortriptyline, and imipramine are the most evidence-based medications for use during breastfeeding; nortriptyline, paroxetine, and sertraline may be preferred choices in breastfeeding women. Use of imipramine during breastfeeding is not recommended by the manufacturer [175]. The lack of adverse effects among infants exposed to fluoxetine justifies its use, especially if prescribed during the pregnancy or if there is a preferential response history. However, its use during breastfeeding is not recommended by the manufacturer [175]. The TCA doxepin should be avoided due to a case report of infant respiratory distress [175]. Data on citalopram, fluvoxamine, bupropion, and venlafaxine are more limited and their use cannot be recommended during breastfeeding [175]. One study evaluating the potential consequences of TCA exposure through breast milk followed exposed children through preschool age and found that exposed children were developmentally similar to non-exposed children. No similar studies have been performed with SSRIs [21].

SUICIDE

For the past 50 years, suicide prevention research has focused on identifying demographic and clinical factors that reliably predict suicide risk. Examining population-level data, researchers found clinical and demographic factors that correlated with suicidality [349]. These variables, including depression, most psychiatric disorders, trait impulsivity, family history of suicide, previous suicide attempts, and current suicidal ideation, became established as suicide risk factors [350; 351]. Suicide risk assessment intends to reduce clinician uncertainty of short-term patient risk of suicide so patients at imminent risk can receive rapid intervention [352; 353]. Decades-old convention holds that assessing suicide risk should culminate in a probability judgment of "low," "moderate," or "high" risk level [349]. Obtaining larger amounts of patient information was believed to be the best means to identify risk factors and reduce uncertainty [353; 354].

However, there is evidence that challenges these foundational assumptions of suicide, including risk factors and risk stratification, long-standing organizing principles of clinical suicide prevention. A 1983 study first identified the limitations of risk factors in suicide prediction, finding that 96.3% of high-risk suicide predictions were false positives and more than 50% of suicides occurred in low-risk patients (false negatives) [355]. Subsequent studies confirmed these results, demonstrating that the clinical reliance on traditional suicide risk assessment, risk factors, and scales were largely overstated [356; 357; 358; 359; 360; 361; 362; 363].

Traditional suicide risk factors are nonspecific, common, non-modifiable, and to varying degrees represent underlying vulnerabilities. These risk factors demonstrably predict lifetime and 12-month suicide ideation, but fail to predict suicide completion, suicide, or movement from ideation to suicide behavior [352]. Many patients have elevated risk profiles, but their lifetime odds of suicide are remote. No study using population-based risk factors or combinations, rating scales, or assessment instruments has successfully predicted suicide in individual patients [350; 351; 364; 365; 366]. The failure to improve suicide prevention and the limited benefit of suicidality interventions suggest inadequate understanding of the mechanisms leading to suicidal behavior [367].

Acute suicide risk is now thought to result from recent psychosocial stressors superimposed on non-modifiable (traditional) risk factors, with psychosocial stressors the precipitants or "triggering events" to suicidal behaviors [364; 368]. Warning signs, or the acute patient response to precipitants, are considered more useful to assess than risk factors [368]. The strongest suicide risk factor—previous suicide attempts—is a static, non-acute factor with low predictive power [369]. While nearly half of suicides made previous attempts, only 5% to 15% of attempters ultimately die by suicide [370; 371]. This

SUICIDALITY IN ADULTS IN THE UNITED STATES, 2021			
Demographic Group	**Past-Year Suicidal Thoughts**	**Past-Year Suicide Plans**	**Past-Year Suicide Attempts**
All adults	12.3 million (4.8%)	3.5 million (1.4%)	1.7 million (0.7%)
18 to 25 years of age	13.0%	4.9%	0.7%
26 years of age and older	3.6%	0.9%	0.4%
50 years of age and older	2.0%	0.3%	0.1%
Males	4.5%	1.3%	0.6%
Females	5.2%	1.5%	0.8%
Past-year use of alcohol or illicit drugs	5.7%	1.7%	0.8%
Past-year use of any illicit drug	11.0%	3.5%	2.0%
Methamphetamine use	15.0%	7.4%	5.3%
Tranquilizer misuse	19.4%	8.7%	5.0%
Cocaine use	16.7%	6.4%	4.2%
Cannabis use	10.9%	3.4%	1.8%
Past-year substance use disorder	21.8%	8.46.0%	4.4%
Past-year major depressive episode	31.8%	11.2%	5.4%
Treated for suicide attempt(s)			
Population	**Any Medical Attention**		**Hospitalization**
All adults	106,000 (4.3%)		87,000 (4.1%)
18 to 25 years of age	4.46%		3.89%
26 to 49 years of age	Not available		Not available
50 years of age and older	Not available		Not available
Source: [15]			*Table 6*

seems a robust predictor, but with distribution of risk across the lifespan, even this risk factor does little to inform of acute patient risk level in any given contact [369].

EPIDEMIOLOGY

Suicide rates declined 24% between 1977 and 2000, but then increased 28% between 2000 and 2015. From 1999 to 2015, approximately 600,000 Americans died by suicide [372; 373]. In 2021 alone, 48,183 Americans died of suicide, an average of 132 suicides every day, or one person every 10.9 minutes. Among persons younger than 15 years of age, one suicide occurs every 1.4 hours [374]. Suicide is the 11th leading cause of death in the United States, and the third leading cause for youth 14 to 18 years of age. The annual cost of suicide in the United States is $70 billion [373; 374; 375].

White boys and men accounted for 70% of all suicides in the United States in 2021; the suicide rate in this population is two times greater than that for non-White boys/men. White men 45 to 64 years of age had the highest suicide rate and number of any demographic in 2021 [374]. White girls and women also have markedly higher suicide rates than their non-White counterparts [374].

In 2021, suicide rates by race/ethnicity were highest in American Indians/Alaska Natives, followed by White Americans, Native Hawaiian/Pacific Islander, Black Americans, Hispanic Americans, and Asian Americans [373]. Overall, suicide rates were highest in persons 25 to 34 years of age and 85 years of age or older and lowest in persons 15 to 24 years of age, despite suicide being the third leading cause of death in this age group [373]. The NSDUH found few racial and ethnic differences for suicidality [15].

Suicide rates in urban and rural areas diverged during 1999–2015, especially after 2008. This could reflect more prevalent social isolation, financial hardship, access to lethal means (guns), and limited access to mental health care [372].

Aside from measures of suicide-related deaths, various levels of suicidality among adults have been studied, with suicidal thoughts, plans, and attempts quantified (***Table 6***). Among adults with past-year suicidal ideation, around 1 in 4 plan suicide and 1 in 7 attempt suicide. There are 25 attempts for every suicide, increasing to 100 to 200 attempts per suicide in individuals 15 to 24 years of age and decreasing to 4 attempts per suicide among the elderly. For each male attempt are three female attempts, and there are 3.9 male suicides for each female suicide [374].

PATHOPHYSIOLOGY OF SUICIDAL BEHAVIOR

Suicidality is a distinct, multidimensional clinical condition now thought to result from interactions among biologic, social, and psychologic vulnerability factors, proximal biopsychosocial events acting as precipitants, and epigenetic factors [350; 351; 376]. The pathophysiology of suicide is distinct from comorbid psychiatric diagnoses. Previous research identified underlying processes in suicidal ideation, but assumptions that ideation predicted suicide attempts is now disproven, with efforts focused on identifying the underlying pathways to suicide.

To advance this research, two empirically confirmed models of suicide have been developed. The stress-diathesis model of suicidal behavior describes long-term vulnerability to suicide, activated by psychosocial or psychiatric crises [376]. The interpersonal theory of suicide proposes desire and capability as the principal factors contributing to suicidal behavior. Suicidal desire is explained by high levels of burdensomeness (i.e., a belief one is an unwanted burden to family/peers) and thwarted belongingness (i.e., social alienation and loneliness). Capability of suicide reflects the sum of noxious stimuli, traumatic events, and experiences of death and pain [377].

Some suicide neurobiology has also been established, such as associations between suicide and gene variations in the HPA axis, serotonin systems, noradrenergic systems, and polyamines that promote functional alterations. In the absence of gene variations, gene expression can become altered by exposure to extreme or chronic stress, becoming both cause and effect of neurobiologic response [376; 378].

Abnormal function in several neurobiologic systems is associated with suicidal behavior, including the HPA axis, serotonergic system, and noradrenergic system. Dysfunction of these systems is associated with impaired regulation of anxiety, impulsivity, and aggression, which may result from genetic variation and environmental stressors (and their interaction) [379; 380]. This may lead to dysfunctional information processing, eventually contributing to increased capability of suicide [378; 381]. Immune system dysregulation is also believed to contribute to suicidality, but the role of inflammatory conditions has not been clearly delineated [382].

SUICIDE AND SPECIAL POPULATIONS

Youth

Before 18 years of age, 12.1% of youth report suicide ideation and 4.1% make at least one attempt [383]. In 2019, 534 children died by suicide, a rate of 2.6 for every 100,000 children between the ages 10 and 14 years [384]. Between 2008 and 2015, encounters for suicide ideation or attempt at children's hospitals nearly doubled [385]. The presence of acne is associated with social and psychologic problems and twice the rate of suicidal ideation [386].

College Students

Suicide is the second most common cause of death among college students, with an estimated 1,000 students taking their lives on college campuses each year. More than 50% of college students report having had suicidal thoughts, and another 10% report a serious suicide attempt. An estimated 80% to 90% of college students who died by suicide were not receiving help from college counseling centers [387]. A study published in 2019 from the American College Health Association/National College Health Assessment survey assessed mental health diagnoses and suicidality from more than 67,000 undergraduate students across 108 institutions [388]. According to the results, one in five students have had thoughts of suicide, with 9% making a suicide attempt and 20% reporting self-injury [388]. Students leaving home for college face unique challenges that may increase suicide risk in vulnerable students, including separation from support systems and social networks, academic stress, pressure to succeed, feelings of isolation, poor coping skills, and mental health stigma.

Gender and Sexual Minority Youth

The Centers for Disease Control and Prevention published the first-ever nationally representative survey on the health risks of gay, lesbian, and bisexual high school students in 2016 [389]. Nationwide, 88.8% of students identified as heterosexual, 2.0% as gay or lesbian, 6.0% as bisexual, and 3.2% as unsure of their sexual identity [389]. Overall, sexual minority youth are more likely than their heterosexual counterparts to experience adverse experiences and suicidality (***Table 7***).

Sexual orientation or gender identity harassment and being threatened or injured with a weapon at school are the most damaging forms of school-based victimization for sexual minority adolescents, and these factors have the greatest association with suicidality [390]. For sexual minority youth, risk factors for bullying and violence include social isolation, lack of parental support, lack of safety or support at school, and harmful norms about masculinity and femininity associated with violence against those seen as not masculine or feminine enough [389].

Bullying and violent victimization of youth perceived as violating gender norms can occur through sexual orientation-based victimization (from perceived or actual same-sex attraction) or gender-variant-based victimization (from presentation perceived to resemble gay or lesbian stereotypes) [391; 392]. Heterosexual youth whose appearance, mannerisms, or behaviors are perceived by peers as violating gender norms are also vulnerable to gender-variant-based victimization. This type of victimization is significantly associated with suicidal thoughts and behaviors in middle and high school students and potentially serious psychologic outcomes similar to those experienced by same-sex attracted adolescents [393].

ADVERSE EXPERIENCES AND SUICIDALITY AMONG HETEROSEXUAL AND SEXUAL MINORITY HIGH-SCHOOL STUDENTS		
Adverse Experience	**Percentage of Students Reporting Experience[a]**	
	Heterosexual	**Gay, Lesbian, or Bisexual**
Threatened or injured with weapon (e.g., gun, knife, club) on school property	5.1%	10.0%
Avoided school because of safety concerns[b]	4.6%	12.5%
Cyberbullied	14.2%	28.0%
Bullied on school property	18.8%	34.2%
Forced to have sexual intercourse[c]	5.4%	17.8%
Physical dating violence	8.3%	17.5%
Sexual dating violence	9.1%	22.7%
Probable major depressive episode	26.4%	60.4%
Seriously considered attempting suicide	14.8%	42.8%
Made a suicide plan	11.9%	38.2%
Attempted suicide	6.4%	29.4%
Suicide attempt received medical care	2.0%	9.4%
[a]All rates are past-year unless otherwise stated. [b]In the past 30 days [c]Over the lifetime		
Source: [389]		*Table 7*

Bullying and Cyberbullying

Adults are not immune to victimization from bullying or cyberbullying, but the bulk of research has focused on adolescent and young adult age groups. Bullying is defined as the use of power and aggression to control and distress another [394]. Intentionality, repetition, and abuse of power primarily distinguish bullying from other forms of aggression [395]. Cyberbullying does not induce distress through physical aggression and harm, but through the reach of Internet and social media. The emotional harm can be severe, in part from the ease that humiliating or threatening information, photos, and other content are spread, and by recruitment of other cyberbullying participants [396].

A study of 15,425 high-school students found higher rates of girls being bullied (31.3%) or cyberbullied (22.0%) compared with boys (22.9% and 10.8%, respectively). Suicide attempts were made by 4.6% of those never-bullied, 9.5% of those bullied at school, 14.7% of those cyberbullied, and 21.1% of those victimized both at school and online [397].

Peer victimization in childhood or adolescence can have long-lasting adverse effects. Among 30,436 U.S. soldiers in basic training, more frequent physical assault/theft by childhood peers was associated with increased odds of lifetime suicidal ideation and attempts; more frequent bullying comments/behaviors was associated with increased risk of ideation, planning, and attempts among ideators. Relative to non-exposure, exposure to the most persistent bullying carried a two- to fourfold increase in risk of suicidality [398].

Gender and Sexual Minority Adults

In Western countries, the lifetime prevalence of suicide attempts is 4% among heterosexuals and 17% among sexual minorities [399]. Among sexual minority populations, a history of suicide attempts increases subsequent risk of repeat attempts and fatal outcomes [377; 400]. Reports suggest high suicide attempt rates among gay/bisexual African Americans, gay/bisexual men of lower socioeconomic status, and sexual minority Latinos [401; 402; 403].

Suicidality disproportionately affects gender minorities, who may represent up to 0.5% of the adult population. Transgender men and women are roughly 5 times more likely to attempt suicide and 19 times more likely to die by suicide than cisgender adults [404]. The suicide attempt prevalence in trans populations is 22% to 43% for lifetime and 9% to 11.2% for past-year [405]. Violent victimization, experienced by 43% to 60% of transgender persons, predicts a fourfold increase in suicide risk [404]. Physical assault increases the odds of attempting suicide, but physical abuse directed at gender identity or expression has greater relative impact on suicidal behavior [404]. Experiencing fewer transphobia events has been associated with a 66% reduction in ideation and a 76% reduction in suicide attempts among ideators [405].

Armed Forces and Combat Veterans

The historically low U.S. Army suicide rate began climbing in 2004 and has exceeded the civilian rate since 2009 [406]. In response, the Army has invested significant resources in suicide prevention efforts [369].

In one study, veterans during the Iraq and Afghanistan war era (317,581 deployed to war zones, 964,493 nondeployed) were followed from the time of discharge to 2010. With 1,868 suicide deaths, both veteran cohorts had 41% to 61% higher risk of suicide relative to the general population, but suicide risk was not associated with a history of war zone deployment and multiple deployments were not associated with greater suicide risk among deployed veterans [407].

Among U.S. Armed Forces veterans, the estimated lifetime prevalence of suicide ideation was 12.7% for men and 20.1% for women, and the prevalence of lifetime suicide attempts was 2.5% and 5.1%, respectively [408]. Among active Armed Forces suicide decedents, roughly 50% accessed health care in the month before their death and more than 25% accessed care in the week before their death. Male, never married, and non-Hispanic Black individuals were less likely to access care prior to death. The number of mental health encounters was the only predictor of suicide risk documentation among decedents at 4 weeks and 52 weeks prior to death [409].

Incarcerated Individuals

Jails and juvenile justice facilities have suicide rates higher than the national averages, and suicide is often the single greatest cause of death in correctional settings. Inmates at highest risk are young men, persons with mental illness, those who are socially disenfranchised and socially isolated, individuals with substance use disorders, those who have previously attempted suicide, gender/sexual minorities, and juveniles placed in adult correctional facilities [410]. Factors that increase suicidal risk include the psychologic effects of arrest and incarceration; intense stressors of prison life, including physical and sexual predation and assault from other inmates; and absence of formal policies for managing suicidal patients, staff training, or access to mental health care [411].

At greatest suicide risk are young (i.e., 20 to 25 years of age), unmarried, male, first-time offenders arrested for minor, usually substance-related, offences. Typically intoxicated at the time of arrest, these individuals tend to attempt suicide at an early stage of confinement, often within the first few hours, from the impact of sudden isolation, shock of imprisonment, lack of information, and fear about the future [411]. This suggests an important role for medical assessment of substance abuse and suicide proneness and inmate suicide prevention programs [31; 412].

SUICIDE AND PUBLIC PERCEPTION

Stigma often surrounds persons with suicidal behavior and suicide itself. Stigma and negative attitudes interact with postmortem determinations and media reporting, and stigma can be antecedent or consequence.

Misclassification of Suicide Deaths

Suicide determinations are not easy, even after the event, and coroners vary considerably in the verdicts they give to individuals who probably died by suicide [360]. Stigma can influence under-reporting, with families or physicians hiding evidence. Death determination may be judged by variable local standards, and ambiguous cases involving suicide may be classified "accidental" or "undetermined" deaths [413]. Context can influence how ambiguous cases of suicides are classed. Institutions such as prisons, hospitals, and religious orders may consider a suicide less embarrassing than homicide. Despite substantial doubt, declaring death a suicide can be motivated by the required investigation of homicide and apprehension of a murderer and negligence lawsuits with accidental death [413].

Suicide Reporting in the Media

Especially among youth, suicide rates may temporarily spike with intense coverage of a suicide in media reports or movies and television [414; 415; 416]. Imitation is the core factor, which is most powerfully illustrated by highly publicized suicides of celebrity figures [417].

Media coverage of suicide can misinform by attributing suicide to a single event (e.g., job, relationship loss) without acknowledging a broader context of ongoing depression, substance abuse, or lack of access to treatment for these conditions. The time from media exposure to action is brief, typically a few minutes. This gives media outlets little time for mitigating actions after population exposure to a harmful story, stressing the need to evaluate news items before publication [418]. Responsible suicide coverage can educate audiences about the causes, warning signs, treatment, and prevention of suicide [414].

Shortcomings are also found in media reporting of cyberbullying-related suicide. Few media outlets follow guidelines to protect against suicidal contagion. Few reports reference suicide or bullying prevention resources, and most suggest suicide has a single cause. A subset of reports uses individual suicides as cautionary tales to elevate cyberbullying awareness [419].

Stigma and Suicide

The stigma of mental illness and substance abuse, both closely linked to suicide, prevents many persons from seeking help over fears of prejudice and discrimination [420]. People with a substance use disorder face added stigma over prevalent beliefs that addiction is a moral failing of persons capable of controlling these behaviors [31; 421]. The stigma of suicide inhibits many from seeking treatment. Family members of suicide attempters often hide the behavior from friends and relatives,

believing it reflects badly on their own relationship with the attempter or that suicidal behavior itself is shameful or sinful. These same feelings are held by many who attempt suicide [31]. Systemic, persistent stigma contributes to inadequate funding for preventive services and insurance reimbursement for treatments, perpetuates under-treatment of substance use and mental health disorders, limits access to tailored services, and maintains unnecessarily high suicide rates [31].

Holiday Suicide Myth

The idea that suicide is more frequent during the holiday season is a debunked myth partially perpetuated by the media [373]. Suicide rates are lowest in December and highest in the spring and fall [422]. The holiday suicide myth is important to counter because it provides misinformation about suicide that may interfere with prevention efforts [423].

SUICIDE MODELS AND RISK FACTORS

As discussed, the lack of predictive value for risk factors is now recognized [424]. The predictive disparity of traditional suicide risk factors (strong for ideation, poor for behavior) suggests that development of suicide ideation and movement from ideation to potentially lethal attempts are distinct processes, with distinct explanations and predictors. This has prompted efforts to identify novel, more effective risk factors guided by strong theoretical models [350; 425].

Other lines of research have identified the need to address acute and immediate factors influencing suicide risk. Many patients have long-term (i.e., one to five years) ideation or tentative planning before a suicide attempt, but almost all proximal planning occurs within two weeks and the majority occurs within 12 hours of a suicide attempt [426]. Assessment of outpatients with past-year suicide attempts and inpatients admitted for suicidality over two to four weeks showed suicidal ideation, hopelessness, burdensomeness, and loneliness varied dramatically over the course of most days in nearly all patients [427].

The suicide prevention field is in transition. Suicide risk factors, assessment tools, and risk level stratification are largely ineffective in short-term prediction of suicide but have not yet been replaced by more effective methods. Resources for suicide prevention are available from the CDC at https://www.cdc.gov/suicide/resources.

The Interpersonal-Psychological Theory of Suicide

The Interpersonal-Psychological Theory of Suicide posits that persons will not make lethal suicide attempts unless they have developed the desire (i.e., low belongingness, high burdensomeness) and ability to do so [377]. Thwarted belongingness is defined as the experience of having little or no social connectedness, a result of living alone, death of a spouse, or disabling physical or psychiatric illness. The need to belong is a core aspect of human nature; when unfulfilled, suicide risk increases [428]. Perceived burdensomeness is evident when persons feel their family members and the world in general would be better off if they were no longer living, and this can initiate suicidal ideation [428]. Acquired capability for suicide refers to reaching the point at which a patient overcomes his or her innate fears of pain, injury, and death with suicide. Opponent process theory suggests with repeated exposure, the effects of previously noxious, aversive, or provocative stimuli may recede, and the opposite effect of the stimuli becomes strengthened and amplified [429]. Persons can habituate to pain, injury, or death through previous suicide attempts, exposure to trauma, armed combat, violence, or death and diverse experiences related to psychologic and physical pain [350; 351].

The Cubic Model

The cubic model defines psychologic pain—psychache—as one of three essential dimensions in suicide risk (along with stress and perturbation) [430]. Psychache often underlies the desire to escape from unbearable pain and represents a state of anguish sufficiently aversive to over-ride innate fears of pain, injury, and death [351]. Psychologic pain distinguished attempters from ideators among 378 adults with history of suicidality [350].

Non-Suicidal Self-Injury

Non-suicidal self-injury (NSSI) is intentional, non-socially accepted damage to the bodily surface, without suicidal intent, by cutting, scratching, hitting/banging, carving, or scraping. Roughly 17% to 18% of teens have one or more NSSI event; up to 60% of adolescent psychiatric patients have one NSSI event and 50% have repetitive NSSI [431; 432]. NSSI prevalence is higher in girls and women. It rises from late childhood to early adolescence, peaks in mid- to late-adolescence, and generally declines by young adulthood [383]. NSSI can occur without a psychiatric diagnosis [433].

NSSI serves as a means to escape aversive emotional (e.g., sadness, anxiety) or cognitive (e.g., negative thoughts or memories) states, relieve tension or anger, or regain perception of control [383; 434]. Adolescents with repetitive NSSI remain at high risk of dysfunctional emotion regulation strategies after ceasing the behaviors and show increased substance abuse as the behaviors decrease [435]. Those who cut themselves on body areas other than arms or wrists have the greatest risk of subsequent suicide [436]. Identifying with "goth" or "emo" youth subculture, sexual minority status, social media exposure to self-injury behaviors, bullying, and childhood emotional abuse are risk factors for NSSI [437].

There is a temporal relationship between nonsuicidal and suicidal self-injury in adolescent outpatients and inpatients. On average, suicide ideation occurs before initial NSSI behavior, suggesting that pathways to NSSI and suicidal behavior may occur simultaneously rather than sequentially from nonsuicidal to suicidal self-injury. The transition from nonsuicidal to suicidal self-injury is relatively fast, and a key period for intervention and prevention is within the first 6 to 12 months after the onset of suicidal thinking [438].

Chronic Pain

Chronic uncontrolled pain is second only to bipolar disorder as a medical cause of suicide [439; 440; 441]. The distress, exhaustion, and hopelessness of chronic unrelieved pain can invite intended overdose. Death is no longer feared, but instead becomes a welcome prospect of permanent relief from suffering and anguish [442]. Individuals with physical pain are substantially more likely than those without pain to report lifetime death wish; to have current and lifetime suicidal ideation, plans, and attempts; and to die from suicide. Chronic uncontrolled pain is a consistent risk factor for suicidality, even after controlling for demographics and psychiatric and substance use disorders [443; 444].

The perception of being a burden significantly predicts wishing to die, active suicide ideation, presence of a suicide plan, history of suicide attempts, and preference for death over disability in patients with chronic pain [445]. Chronic uncontrolled pain elevates the risk of suicide to escape unbearable suffering, in part by promoting (or becoming amplified by) depression and hopelessness. This intensifies a desire to escape that erodes the natural fear of dying, promoting the development of fearlessness about death—a key risk factor for suicide [446].

Psychologic Pain

Suicide is viewed as behavior motivated by the desire to escape from unbearable pain, and suicide risk research implicates two related constructs: psychache and pain tolerance, defined as the greatest duration or intensity of painful stimuli one can withstand before pain is intolerable and unbearable [447; 448]. Psychache is a crucial link between suicidal risk and behavior and mediates the relationship between depression or other psychologic conditions and suicidality [447; 448; 449; 450; 451]. As discussed, numerous studies indicate that psychache highly predicts suicidality and distinguishes attempters from ideators. Changes in suicide preparation and intent over three years significantly correlates with changes in psychache but not depression or hopelessness [452]. Evidence links pain tolerance to self-injurious behaviors and suicide risk. Psychache and physical pain are linked to other predictors of suicide, including impaired reward processing, hopelessness, and depression [448].

Mental pain is a uniquely intolerable experience that exceeds the sum of negative emotions, thoughts, and sensations. Beliefs can develop that change or improvement is not possible and self-destruction is the only resolution [447; 453]. Unbearable, persistent psychologic pain is also thought to reduce awareness of the body and its signals, making it more likely to perceive the body as an object and an easier target to attack [454].

Among patients in residential treatment with serious psychopathology, history of suicide ideation or attempts is associated with proportionally greater psychic pain and fewer reasons for living. Treatment of such patients should include both an understanding of the sources of psychic pain and promotion of individual discovery of reasons for living [455].

Psychiatric Disorders

Traditional suicide risk factors include mood (e.g., bipolar disorder, MDD), anxiety, impulse control, personality, psychotic, and alcohol/substance use disorders [368]. There is little evidence that trait impulsivity increases risk of attempts in ideators, although suicidal behavior can occur during transient impulsive states [456]. In patients with MDD, the condition most associated with suicide, the lifetime suicide prevalence is 4% for hospitalized individuals, 2.2% in mixed inpatient/outpatient populations, and 8.6% if hospitalized for suicidality [66]. However, it is important to remember that MDD alone does predict acute risk of suicide, and depression and most psychiatric disorders alone do not predict transition from ideation to suicidal plans or attempts.

Acute Anxious Agitated Distress

While symptomatic panic disorder, PTSD, and generalized anxiety disorder influence suicide behavior more than any other psychiatric disorders, it is the acute state of anxious agitated distress (not an anxiety disorder diagnosis) that greatly increases risk of ideators moving to suicide attempts [368; 457]. Among inpatient suicides, 79% met diagnostic criteria for severe or extreme anxiety and/or agitation.

Anxious agitated distress is characterized by intense/severe anxiety, agitation, or panic and mental anguish and unrest with restless or repetitive behaviors, heightened arousal, expressions of emotional turmoil, irritability, anger outbursts, insomnia, and nightmares [351; 368; 409; 458; 459]. It is commonly observed immediately before suicide and is a documented precursor of near-fatal attempts. Clinicians should inquire regarding perceived anxious agitated distress and may ask patients if they feel like "jumping out of their skin" or "going to explode" or if feel they must "take action" or "do something" from overwhelming inner restlessness.

Bipolar Depression

An estimated 5 to 10 million Americans currently suffer from bipolar disorder. Bipolar depression is the depressive phase of bipolar disorder, when suicidal behavior is most frequent but least responsive to standard treatment. On average, patients with bipolar disorder spend three times longer in the depressive phase than in the manic phase. It is a highly disabling disorder, causing marked occupational and social impairment. Patients with bipolar depression have a 25% to 56% lifetime prevalence of suicide attempts, and 10% to 19% die by suicide [460].

Alcohol and Substance Use Disorders

More than 33% of suicides occur during alcohol use, typically at high levels of ingestion, and controlled trials confirm that acute alcohol use is a potent suicidal risk factor [461; 462; 463; 464]. Alcohol intoxication significantly increases suicide risk and may heighten psychologic distress and aggression, encourage suicide attempts, and inhibit adaptive coping strategies [465]. During intoxication, disinhibition facilitates movement

from ideation to impulsive action, and alcohol intoxication predicts use of lethal means in suicide [465; 466]. However, substance use disorder and suicidality can be temporarily linked, as patients are likely to deny suicidality after intoxication has resolved [467; 468].

Psychotic Disorders

Suicide is the greatest cause of premature death in individuals with schizophrenia, with the highest risk in young, unemployed men. Other risk factors include recurrent relapses, fears of deterioration in persons with high intellectual ability, positive symptoms of suspiciousness and delusions, and depressive symptoms [469; 470]. The suicide risk is greatest during early-stage illness, early relapse, and early recovery; risk declines with prolonging illness duration [469; 470].

Persecutory panic (a state of terror often associated with command hallucinations and delusions) has been observed in many psychotic disorders. These patients are described as terrified of a threatening and imminent annihilation or dismemberment, imagine that suicide is survivable, and desperately attempt to escape from the danger of imaginary menace by suicide [471]. Therefore, the presence of persecutory panic is considered a risk factor for suicide and should be addressed immediately.

SUICIDE MEANS AND METHODS

In 2021, firearms were the most common means used in suicide deaths (54.6%), followed by suffocation/hanging (25.8%) and poisoning (11.6%) [374]. In the United States, the rate of suicide by firearm is eight times greater than the rates in other economically developed countries [472]. Household gun ownership strongly correlates with firearm suicide, and storage practices impact suicide rates, which are higher in geographic areas with greater household prevalence of loaded guns. The presence of loaded, unlocked firearms within reach is a risk factor for fatal outcomes from suicidal behavior [473].

Suicide by cop is defined as an event in which a suicidal subject intends to die and, aware of the finality, directs behavior against police that is sufficiently life-threatening to compel a deadly force response [474]. Although usually intending to die, the subject is ambivalent about taking his or her own life. Suicide by cop victimizes the suicidal subject, and the police who are often placed in near-impossible situations. In 707 officers-involved shootings between 1998 and 2006, 36% were attempted suicides and 51% of subjects were killed [475]. Suicide by cop is characterized by one of the following [475; 476]:

- Direct confrontation: The attack on police is premeditated with intent to die from a deadly force response.
- Disturbed intervention: Emotionally disturbed behavior that draws police intervention, without evidence of wanting police involvement.
- Criminal intervention: A criminal, believing there is no way out, prefers death to arrest and incarceration.

SUICIDE MOTIVATION

Most suicides and attempts are driven by the motivation to escape unbearable pain. Other motives include revenge, shame, humiliation, delusional guilt, command hallucinations, gaining attention or reaction from others, loneliness, self-hatred, or a sense of being a burden, not belonging, feeling trapped, or having no purpose [364]. Individuals have a unique balance between their personal motivations for suicide and their reasons for living. Reasons for living can include religious beliefs, a sense of responsibility to children or others, plans for the future, or a sense of purpose in life. A strong social support network is also protective against suicide [364]. Importantly, "reasons for living" become irrelevant when suicidal intent is moderate or greater.

SUICIDE PREVENTION

Large-scale suicide prevention efforts in the United States began in 1958 with the first suicide prevention center in Los Angeles, followed by nation-wide crisis intervention centers [31]. The risk factor approach to suicide prevention was introduced in 1966; organizations and national strategies were established to further these efforts. Survivors of suicide started the Suicide Prevention Advocacy Network USA (SPAN USA) in 1996 to campaign for a national suicide prevention strategy, prompting the creation of the National Strategy for Suicide Prevention (NSSP) in 2001 [477].

Recognizing that decades of suicide prevention research has not decreased suicides, the NSSP partnered with the National Action Alliance for Suicide Prevention in 2012 to develop national priorities for suicide prevention science. Suicide research was prioritized to delineate promising research pathways toward a set of 12 "aspirational goals" considered areas of focus necessary for preventing substantial numbers of suicide deaths and attempts [478].

The revised NSSP was launched in 2013, elaborating on methods for systemic change in healthcare delivery, public and media conversations around suicide and suicide prevention, the timeliness and utility of suicidality surveillance data, prevention, and clinical care [479]. "Zero suicides" is an aspirational goal based on the belief that suicide of patients receiving care in any setting is preventable, and one area of commitment is to program approaches that prevent suicidal patients from failing to receive adequate care. In 2014, the NSSP launched the Framework for Successful Messaging, which outlines how individuals working in suicide prevention and behavioral healthcare fields can create hopeful messaging to help save lives. In 2015, the NSSP and partners offered a three-panel series focused on suicide in middle-aged men, teenagers and technology, and military personnel/veterans [479]. Universal suicide risk screening in primary, specialist, and emergency care settings was recommended [480].

Suicide Prevention in the Elderly

The elevated suicide risk in the elderly is influenced by the prevalence of isolation, chronic pain, chronic illness, and/or depression (often undiagnosed). Many at-risk elderly adults suffer from intense loneliness, bereavement, or loss of social roles; fears of disability, dependency, or burdensomeness to others are common [481]. Enhancing connectedness to others is a suicide protective factor and formal strategy to prevent suicide in the elderly [480].

TREATMENT OF SUICIDALITY

Psychotherapy

Highly structured, problem-solving, coping-oriented psychotherapies have the greatest research support for effectively treating suicidal risk, and include dialectical behavioral therapy, cognitive therapy, and collaborative assessment and management of suicidality [482].

Dialectical behavioral therapy is the most thoroughly studied and effective psychotherapy for suicidal behavior. It has been shown in multiple studies to decrease suicide attempts, self-harm, and other suicide-relevant markers such as suicidal ideation and hopelessness. This psychotherapy emphasizes skills training and mindfulness-based emotion regulation [482].

Cognitive therapy is the next most studied and supported suicide-relevant psychotherapy. The initial randomized controlled trial of suicide-specific cognitive therapy in persons presenting to the emergency department with suicide attempt gave convincing evidence that 10 sessions decreased follow-up suicide attempts compared to the control group. The primary focus of this modality is identification of patient "suicidal mode," activated by certain experiences, memories, thoughts, and situations. Patients learn what triggers their suicidal mode and develop and use alternate non-suicidal coping responses [482].

Collaborative assessment and management of suicidality is a therapeutic framework that emphasizes collaborative assessment, crisis response planning, and problem-focused interventions designed to identify and treat the "drivers" of suicidal risk. In one study, it was shown to effectively treat suicidal ideation, overall symptom distress, hopelessness, and reasons for living at 12-month follow-up compared to enhanced usual care [482].

Pharmacotherapy

Effective pharmacotherapy for suicidality has been elusive. Antidepressants are standard treatment for acutely suicidal patients, but delayed onset imposes unacceptable distress and elevates risk of lethal self-harm [47]. In MDD and bipolar disorder, lithium is protective against suicidal behavior and has extensive evidence support, but it is underprescribed for this purpose. In schizophrenia, clozapine is superior to other antipsychotic agents in lowering suicide rates. However, the need for close toxicity monitoring has limited its use in preventing suicide. In severe MDD with high suicide risk, ECT is established as rapid, effective treatment, but practical issues and stigma constrain its use [47; 483; 484].

Aside from clozapine and lithium, pharmacotherapy approaches have traditionally been based on the belief that suicidality is an extension of MDD [485]. However, breakthroughs have been made in rapid-active drug interventions for suicidal individuals, with ketamine, esketamine, and buprenorphine now being explored for this use [485; 486; 487; 488; 489; 490; 491]. In 2016, the FDA granted breakthrough therapy designation for intranasal esketamine in patients with MDD at imminent risk for suicide [321]. A study published in 2020 found that esketamine nasal spray demonstrated rapid and robust efficacy in reducing depressive symptoms in severely ill patients with MDD who had active suicidal ideation with intent [492].

ASSESSMENT OF SUICIDE RISK

Standard suicide risk assessment intends to gather clinical information sufficient to determine patient risk level for suicide, culminating with clinician estimation of risk based on suicide thoughts, intent, behaviors; protective and risk factors, precipitants, warning signs; and behavioral observation during assessment [364; 366; 368]. Patients with any of the following conditions should be assessed for suicide risk, although many are nonspecific factors that do not predict current risk [364; 366; 368]:

- Psychiatric (e.g., MDD, bipolar depression, schizophrenia, PTSD) and medical (e.g., chronic pain, sleep disturbance, frequent headaches) disorders
- Positive depression screening results (e.g., very high scores, suicidality concerns, suicidal thoughts in perinatal women)
- Patients seeking help or self-reporting suicidal thoughts
- Referrals from close others over concerns about patient behavior
- Clinical judgment

Eliciting Information

Guidelines recommend an empathetic and direct, yet objective and non-judgmental, approach to eliciting information from patients believed to be at risk for suicide. The gravity of high acute suicide risk and vital need for information suggests an assertive approach. The following recommendations have been made for these situations [364; 493]:

- Be clear and use specific, open-ended questions. Be flexible to frame questions more clearly.
- Avoid assuming patients and families understand clinical terms, even if clarification is not requested.

ACUTE SUICIDE RISK LEVEL AND INTERVENTION			
Risk Level	**Contributing Factors**	**Suicidality Level**	**Possible Interventions**
High	Acute, severe psychiatric illness or symptoms Acute precipitating event	Lethal attempt Ideation, strong intent to act/plan Cannot control impulses Rehearses/prepares suicide	Continuous observation; limit access to lethal means; immediate transfer to emergency department for hospitalization
Moderate	Multiple warning signs or risk factors	Ideation No intent to act Impulse control intact	Prompt referral to mental health clinician Limit access to lethal means
Low	Risk factors modifiable Protective factors strong	Ideation No plan, intent, behavior	Outpatient referral Give emergency/crisis numbers

Source: [364; 366; 368] *Table 8*

- Ask for clarification, and do not accept vague answers. Ask follow-up questions.
- Document positive and negative specifics carefully, in narrative form.

Clinical suicide assessment guidelines give little attention to dealing with patients suspected of being at acute risk for suicide who are unable or unwilling to cooperate with the risk assessment process. Patients evaluated for suicide are often in crisis and may fear that sharing their suicidality will result in loss of autonomy through hospitalization, behavioral restriction, or loss of esteem from a psychiatric diagnosis. In response to these fears, patients can minimize or deny their suicidality when directly asked or make statements to decrease clinician vigilance; clinicians should be aware of these tactics [366].

Thinking and cognition are often clouded, and intentionally or not, many patients with increased suicide risk give inaccurate, incomplete, and unreliable histories. Patients can misunderstand their symptoms, condition, and risk and usually cannot predict their impulses and behaviors [493; 494]. Clinicians often believe suicidal patients view them as allies, but they are more likely seen as adversaries with conflicting goals: preserving versus ending life. This is a fundamental change in the patient-provider relationship after a patient decides to attempt suicide [494].

As such, alternative lines of evidence may be necessary to confirm suspicions of suicide risk, including obtaining objective evidence and collateral information/permissions [493; 494]. Patients who attempt suicide may communicate intent to relatives before clinicians [494]. Among inpatients who die by suicide, 78% denied suicidal ideation in their last communication with staff, 60% told their spouse, and 50% told other relatives; however, only 18% told their physician [459]. Other providers, relatives, and close others can be vital information sources to help ascertain acute suicide risk level and are often more reliable than severely suicidal patients.

Assessing Suicidality

As discussed, many areas of patient information emphasized by standard practice guidelines as crucial for patient risk assessment have been found to lack risk prediction value. Instead, clinicians should focus on critical factors related to suicide risk, identified by studies of callers to suicide prevention hotlines, including [493; 495]:

- Suicidal desire: Suicidal ideation, psychologic pain, hopelessness, helplessness, perceived burden to others, feeling trapped, feeling intolerably alone
- Suicidal capability: History of suicide attempts, exposure to someone else's death by suicide, available means of killing self/others, current intoxication, substance abuse, acute symptoms of mental illness, extreme agitation/rage
- Suicidal intent: Attempt in progress, plan to kill self/others, preparatory behaviors, expressed intent to die

Suicide Warning Signs: Indications for Urgent/Immediate Action

Suicide warning signs are recent, unusual changes in the patient, often an acute response to precipitants, and proximally associated with imminent suicide risk. Intent may be signaled through emotions, thoughts, or behaviors. Danger is elevated with previous suicide attempts, family history of suicide, or possession of a lethal method. Presence of any of the following warning signs requires immediate attention, mental health evaluation, and possibly hospitalization to ensure patient safety, stability, and security:

- Suicide communication—threatening to harm or kill self
- Preparations for suicide
- Seeking access, or recent use, of lethal means

Other warning signs may further elevate acute suicide risk include [366; 368]:

- Verbalizations: Hopelessness (feeling of defeat, that nothing can improve their situation), purposelessness (sense of purpose or reason to live is absent), feeling trapped (no way out, no escape possible), or guilt/shame (overwhelming self-blame, remorse, self-hatred)
- Behaviors: Anger, rage, revenge-seeking, reckless/impulsively risky behavior, marked mood changes, anhedonia, withdrawal from family, friends, society
- Inability to sleep
- Command hallucinations

Acute Suicidality Risk Level and Intervention

After a patient's suicide risk level has been assessed and assigned, based on clinical judgment, the level of intervention may be selected (***Table 8***).

The Cognitive State

The cognitive/affective state of suicidal patients is typified by ambivalence, impulsivity, and rigidity. The desire to die and live alternates; clinicians may explore ambivalence to reinforce reasons for living. The transient nature of impulse permits clinicians to defuse a suicide crisis by support at an impulsive moment. Rigidity constricts patient thinking, mood, and motivation; perception of problems and outlook is dichotomized into black-and-white reasoning. With gentle reasoning, clinicians may help the patient understand and consider alternative options to death [469; 470].

Acute Anxious Agitation

Treat patients with anxious agitated distress states aggressively with benzodiazepines and/or antipsychotics, considering age and past/current medication exposure. Frequently monitor these patients for efficacy and side effects, and strongly consider emergency evaluation [368; 496].

Safety Precautions

In all clinical settings, scrutinize patient belongings and nearby medical equipment, such as intravenous tubing, for use in self-harm. Decline family or friends' insistence on driving patients to treatment; transfer patients for emergency evaluation or hospitalization safely by ambulance with trained personnel following standard protocols. During hospital or emergency department discharge or outpatient visits, recommend that close others secure or remove firearms, large quantities of medication, and other obvious means of self-harm. Make an effort to involve family and significant others in crisis planning and treatment [368].

Suicide Prevention Contracts

Written and verbal "no harm" and "no-suicide" contracts do not prevent suicide and tend to give clinicians a false sense of safety that decreases vigilance and may communicate an uncaring "brush-off" to patients, especially in busy clinics and emergency departments. In one study, approximately 50% of inpatients who died by suicide had a prevention contract in place. It is recommended that suicide prevention contracts not be used [366; 493; 497; 498; 499].

SUICIDE LOSS SURVIVORS

Suicide loss survivors are those family members and friends affected by the death of a loved one through suicide. Estimates suggest that each suicide death exposes 147 people, of whom 6 or more experience a major life disruption. With 948,090 suicide deaths in the United States between 1997 and 2021, there are more than 5.69 million suicide loss survivors [374].

The death of a loved one by suicide can be shocking, painful, and unexpected for survivors, with significant impact on health and mental health. A Danish study found that within five years of the loss, spouses bereaved by a partner's suicide had higher risks for mental disorders, suicidal behaviors and mortality, use of public assistance, and mental health care utilization than spouses bereaved by other manners of death [500]. The ensuing grief can be intense, complex, chronic, and nonlinear.

Working through grief is a highly individual and unique process that survivors experience in their own way and at their own pace. Grief does not always move in a forward direction, and there is no timeframe for grief. Survivors should not expect their lives to return to their previous state and should strive to adjust to life without their loved one. The initial emotional response may be overwhelming, and crying is a natural reaction and an expression of sadness following the loss of a loved one [481].

Survivors may struggle to comprehend why the suicide occurred and how they could have intervened, and the guilt over perceiving missed opportunities with hindsight can be agonizing. Relief may be felt if the loved one was prone to difficult mood or temperament. The stigma and shame surrounding suicide may inhibit family members and friends from contacting survivors and can prevent survivors from reaching out for help. Ongoing support remains important to maintain family and relationships during the grieving process [481].

Many survivors find support groups for suicide loss survivors the most beneficial means to feel supported and understood. The shared experience of group members enables survivors to openly discuss their story and feelings without pressure, fear of judgment, or shame [481].

The American Foundation for Suicide Prevention maintains an international directory of suicide bereavement support groups on their website at https://afsp.org/find-support.

CONCLUSION

Depression is a debilitating and potentially life-threatening mood disorder that afflicts millions of Americans. Depressed persons are more likely to develop chronic medical conditions, including type 2 diabetes and cardiovascular disease, and depression is projected to be the leading cause of disability over the next 20 years. Furthermore, suicide is a major preventable public health problem and cause of mortality. Depression, especially with comorbid substance abuse, represents a significant risk factor for suicide. Depression causes enormous pain and suffering to the afflicted and substantial economic cost to society, and the emotional impact on survivors of a depressed person who has died by suicide is often devastating. Many persons with depression do not seek treatment; among those who do, only a fraction receive treatment consistent with current practice guidelines. Primary care contact may represent the last opportunity for intervention in the severely depressed suicidal patient, making the thorough comprehension of identification and treatment of depression and suicide risk imperative.

Customer Information/Answer Sheet/Evaluation insert located between pages 60–61.

COURSE TEST - #96404 DEPRESSION AND SUICIDE

This is an open book test. Please record your responses on the Answer Sheet.
A passing grade of at least 70% must be achieved in order to receive credit for this course.

In accordance with the AMA PRA Category 1 Credit™ system,
physicians must complete and pass a post-test to receive credit.

This 15 credit activity must be completed by July 31, 2026.

1. All of the following statements regarding depression are TRUE, EXCEPT:
- A) *Depression is less common among the medically ill.*
- B) *Women have higher lifetime rates of depression than men.*
- C) *One in 5 Americans are afflicted by depressive disorders annually.*
- D) *Roughly 18.4% of all persons in the United States will have a diagnosable depression at least once in their lifetimes.*

2. Which of the following is a risk factor for depression?
- A) *Being married*
- B) *Higher socioeconomic status*
- C) *Severe underweight in women*
- D) *Major life changes such as job loss or divorce*

3. Maintaining antidepressant therapy following onset of a major depressive episode
- A) *reduces recurrence.*
- B) *delays future recurrences.*
- C) *has no effect on recurrence.*
- D) *may increase the risk of a recurrence.*

4. Persons with MDD are at highest risk of a first suicide attempt
- A) *in the first three months of onset.*
- B) *three to six months after onset.*
- C) *six to nine months after onset.*
- D) *one year after onset.*

5. Major depression can manifest as disturbances in
- A) *appearance and affect.*
- B) *cognition and sensorium.*
- C) *mood and thought process.*
- D) *All of the above*

6. All of the following symptoms occurring nearly every day are diagnostic criteria of MDD, EXCEPT:
- A) *Insomnia or hypersomnia*
- B) *Reckless, impulsive behavior*
- C) *Feeling of worthlessness or inappropriate guilt*
- D) *Loss of interest or pleasure in all or almost all activities*

7. In some cultures, depression and anxiety may be expressed through
- A) *panic attacks.*
- B) *somatic symptoms.*
- C) *psychotic symptoms.*
- D) *delusions of persecution.*

8. Compared to younger adults with depression, the elderly are more likely to exhibit
- A) *sadness.*
- B) *irritability.*
- C) *unhappiness.*
- D) *vegetative signs.*

9. The most frequent comorbid psychiatric condition in patients with a diagnosis of MDD is
- A) *social phobia.*
- B) *generalized anxiety disorder.*
- C) *post-traumatic stress disorder.*
- D) *borderline personality disorder.*

10. Patients with MDD with psychotic features should receive
- A) *an antipsychotic alone.*
- B) *an antidepressant alone.*
- C) *electroconvulsive therapy alone.*
- D) *an antipsychotic and an antidepressant medication or electroconvulsive therapy.*

11. Which of the following general medical conditions does NOT influence the choice of antidepressant drug based on side effect profile or adverse drug-drug interaction?
- *A) HIV infection*
- *B) Chronic asthma*
- *C) Seizure disorders*
- *D) Parkinson disease*

12. The restrictive diet required with oral MAOIs is due to which mechanism?
- *A) Muscarinic receptor blockade*
- *B) Inhibition of dietary amine catabolism*
- *C) Antagonism of intestinal opioid receptors*
- *D) Activation of gastrointestinal serotonin receptors*

13. Which of the following antidepressants is associated with the lowest risk of discontinuation symptoms?
- *A) Paroxetine*
- *B) Fluoxetine*
- *C) Venlafaxine*
- *D) Amitriptyline*

14. If a patient does not adequately respond to initial antidepressant therapy, all of the following options should be considered, EXCEPT:
- *A) Stopping treatment completely*
- *B) Adjusting the treatment plan*
- *C) Re-evaluating the initial diagnosis*
- *D) Optimizing the prescribed therapy*

15. Which of the following is a contributor to treatment-resistant depression?
- *A) Illness severity*
- *B) Medical and psychiatric comorbidity*
- *C) Limitations of FDA-approved drug options*
- *D) All of the above*

16. Which of the following antidepressants is rated pregnancy category D, indicating positive evidence of risk to the fetus?
- *A) Bupropion*
- *B) Paroxetine*
- *C) Venlafaxine*
- *D) Maprotiline*

17. Suicide is especially prevalent among which of the following demographic groups?
- *A) Black boys and men*
- *B) White boys and men*
- *C) Hispanic girls and women*
- *D) Asian/Pacific Islander girls and women*

18. Men are more likely than women to
- *A) attempt suicide.*
- *B) die by suicide.*
- *C) experience depression.*
- *D) seek help for mental health problems.*

19. Which of the following contributes to the high rate of suicide attempts among lesbian, gay, bisexual, and transgender youth?
- *A) Social involvement*
- *B) Greater family support*
- *C) Stigma and discrimination*
- *D) Higher perceived safety at school*

20. Non-suicidal self-injury (NSSI) is
- *A) a means to escape positive cognitive states.*
- *B) rare among adolescent psychiatric patients.*
- *C) unintentional damage to the bodily surface.*
- *D) more common in girls and women than boys and men.*

21. The psychiatric condition most associated with suicide is
- *A) schizophrenia.*
- *B) panic disorder.*
- *C) bipolar disorder.*
- *D) major depression.*

22. Which of the following is TRUE regarding alcohol/drug use and suicide?
- *A) More than 33% of suicides occur during alcohol use.*
- *B) Alcohol intoxication significantly increases suicide risk.*
- *C) Substance use disorder and suicidality can be temporarily linked.*
- *D) All of the above*

Test questions continue on next page ➞

23. In 2021, the most common means used in suicide deaths was

A) firearms.
B) poisoning.
C) suicide by cop.
D) suffocation/hanging.

24. Most suicides and attempts are driven by

A) revenge and shame.
B) command hallucinations.
C) gaining attention or reaction from others.
D) the motivation to escape unbearable pain.

25. Which of the following is a suicide warning sign that requires immediate attention, mental health evaluation, and possibly hospitalization?

A) Inability to sleep
B) Command hallucinations
C) Verbalizations of hopelessness
D) Seeking access, or recent use, of lethal means

Be sure to transfer your answers to the Answer Sheet insert located between pages 60–61.
PLEASE NOTE: Your postmark or facsimile date will be used as your test completion date.

Full Course Availability List

✓	Course #	Course Title/Credits	Price

ALTERNATIVE MEDICINE

☐	98010	Cannabinoid Overview/3	$29
☐	98020	Commonly Abused Supplements/2	$23
☐	98030	Getting to the Point: Acupuncture and Acupoint Therapies/4	$36
☐	98060	Microbiome Medley: Pre-, Pro-, and Postbiotics/2.5	$23
☐	98070	The Scoop on Collagen/1.5	$23
☐	98080	Top-Selling Herbal Supplements/3	$29
☐	98090	Understanding Glucosamine and Chondroitin/1.5	$23
☐	98100	Complementary Therapies for Menopause/4	$36
☐	98120	Diets and Dietary Approaches to Weight Loss/4	$36
☐	98190	Supplements for Aging/5	$43
☐	98210	Medicinal Mushroom Supplements/3	$29
☐	98320	Natural Psychedelics/3	$29
☐	98394	Herbal Medications: An Evidence-Based Review/10	$78
☐	98402	Dizziness and Vertigo/10	$78

COMMUNITY HEALTH

☐	91043	Developing a Safe Opioid Treatment Plan for Managing Chronic Pain/1	$23
☐	91413	Prescription Opioids: Risk Mgmt & Strategies for Safe Use/15	$113
☐	91514	Medical and Illicit Use of Anabolic Steroids/5	$43
☐	91534	A Review of Infertility/10	$78
☐	91544	Metabolic Syndrome: A Growing Epidemic/5	$43
☐	91574	Diagnosing and Treating Overweight and Obese Patients/5	$43
☐	91603	Prescribing Opioids: The West Virginia Requirement/3	$29
☐	91660	Falls and Fall Prevention/3	$29
☐	91694	Families of Patients with Chronic Illness/10	$78
☐	91724	What Healthcare Professionals Should Know About Exercise/5	$43
☐	91743	Child, Adolescent, and Adult Immunization Schedules/5	$43
☐	91753	Chemical and Radiologic Injuries in Terrorist Attacks/1	$23
☐	91764	Bioterrorism: An Update for Healthcare Professionals/5	$43
☐	91784	Smoking and Secondhand Smoke/10	$78
☐	91794	Promoting the Health of Gender and Sexual Minorities/5	$43
☐	91803	Cancer Screening Among Racial/Ethnic Minority Women/5	$43
☐	91923	Clinical Care of the Transgender Patient/10	$78
☐	91943	Providing Culturally Responsive Care for Asian Immigrants/10	$78
☐	91954	Carpal Tunnel Syndrome/3	$29
☐	91984	The Role of Spirituality in Health and Mental Health/5	$43
☐	91993	Cancer Screening/10	$78

ETHICS - HUMAN RIGHTS

☐	47174	Medical Ethics for Physicians/5	$43
☐	97001	Implicit Bias in Health Care/3	$29
☐	97023	Sexual Assault/3	$29
☐	97033	The Intersection of Pain and Culture/5	$43
☐	97081	Sexual Harassment Prevention: The Illinois Requirement/1	$23
☐	97111	Recognizing and Reporting Human Trafficking in Florida/2	$23
☐	97144	Assessment and Management of Pain at the End of Life/2	$23
☐	97281	Pain Management Pearls: Opioids and Culture/2	$23
☐	97364	Cultural Meanings of Death and Dying/5	$43
☐	97384	Palliative Care and Pain Management at the End of Life/15	$113
☐	97430	Cultural Competence: An Overview/2	$23
☐	97440	Implicit Bias: The Michigan Requirement/2	$30
☐	97454	Violence in the Healthcare Workplace/5	$43
☐	97471	Human Trafficking and Exploitation: The Texas Requirement/5	$43
☐	97481	Sexual Harassment Prevention: The California Law/2	$23
☐	97494	Digital Technology and Domestic Violence/3	$29
☐	97501	Imminent Death and Loss/1	$23
☐	97510	Intercultural Competence and Patient-Centered Care/4	$36
☐	97534	Child Abuse Identification & Reporting: The NY Requirement/2	$23
☐	97584	Child Abuse in Ethnic Minority and Immigrant Communities/10	$78
☐	97664	Online Professionalism and Ethics/3	$29
☐	97770	Counseling Patients at the End of Life/5	$43
☐	97791	Domestic and Sexual Violence/5	$43
☐	97824	Elder Abuse: Cultural Contexts and Implications/5	$43

✓	Course #	Course Title/Credits	Price

GERIATRICS

☐	99084	Anemia in the Elderly/5	$43
☐	99090	Alzheimer Disease and Dementias/3	$29
☐	99144	Osteoporosis: Diagnosis and Management/5	$43

INFECTION CONTROL / INTERNAL MEDICINE

☐	48763	Diagnosis & Mgmt of Chronic Kidney Disease in Primary Care/5	$43
☐	48853	Pressure Ulcers: Prevention and Management/10	$78
☐	94040	Monkeypox: The 2022 Global Outbreak/3	$29
☐	94083	Ebola Virus Disease/4	$36
☐	94093	The Mechanism-Based Approach to Pain Management/1	$23
☐	94102	Low Back Pain/15	$113
☐	94111	Pit Viper Snakebite Assessment and Treatment/10	$78
☐	94131	Neck Pain in Adults/10	$78
☐	94151	The Coronavirus Disease (COVID-19) Pandemic/2	$23
☐	94182	Viral Sexually Transmitted Infections/5	$43
☐	94214	Multidrug-Resistant Microbial Infections/5	$43
☐	94223	Hypertension: Strategies to Improve Outcomes/5	$43
☐	94280	Pharmacologic & Medical Advances in Obesity Mgmt/15	$113
☐	94301	Fibromyalgia/3	$29
☐	94344	Diagnosis and Management of Sepsis/4	$36
☐	94364	Malaria and the International Traveler/3	$29
☐	94424	Influenza: A Comprehensive Review/10	$78
☐	94454	Autoimmune Diseases/15	$113
☐	94523	Type 2 Diabetes: Treatment Strategies for Optimal Care/5	$43
☐	94554	Tuberculosis: An Update/5	$43
☐	94614	*Clostridioides difficile* Infection/5	$43
☐	94674	Pneumonia/10	$78
☐	94723	HIV/AIDS: Epidemic Update for Florida/1	$23
☐	94734	HIV/AIDS: Epidemic Update for Washington/7	$57
☐	94902	Gastroesophageal Reflux Disease in Adults/10	$78
☐	94924	Animal-Related Health Risks/15	$113
☐	94934	Rheumatoid Arthritis/5	$43
☐	94954	Osteoarthritis/10	$78
☐	94994	Viral Hepatitis/5	$43
☐	98401	Dizziness and Vertigo/10	$78
☐	98533	Smallpox Vaccination: An Update/5	$43
☐	98593	Multiple Sclerosis: A Comprehensive Review/10	$78
☐	98623	Foodborne Disease/10	$78
☐	98643	Infection Control: The New York Requirement/5	$43
☐	98663	Oral Pathology Review/5	$43
☐	98703	Chronic Pain Syn.: Current Concepts & Treatment Strategies/15	$113
☐	98712	Zika Virus Disease/3	$29
☐	98721	Bacterial Sexually Transmitted Infections/5	$43
☐	98772	Parkinson Disease/10	$78
☐	98783	Healthcare-Associated Infections/15	$113
☐	98793	Food Allergies/5	$43
☐	98813	Chronic Obstructive Pulmonary Disease (COPD)/10	$78
☐	98883	Sleep Disorders/10	$78
☐	98903	HIV/AIDS: Epidemic Update/5	$43
☐	98932	Irritable Bowel Syndrome/10	$78

MANAGEMENT

☐	41032	Burnout in Physicians/5	$43
☐	41170	Professional Boundaries and Sexual Misconduct in Medicine/3	$29
☐	41234	OSHA and Healthcare Facilities/5	$43
☐	41473	Risk Management/5	$43
☐	91012	Family & Medical Leave: Law, Health Care, & Social Services/5	$43
☐	91054	Health 2.0: Implications for Care/3	$29
☐	91140	HIPAA Privacy and Security/5	$43
☐	91283	Using Interpreters in Health and Mental Health Settings/5	$43
☐	91334	Medical Error Prevention and Root Cause Analysis/2	$23
☐	91380	Safe Handling of Hazardous Medications/2.5	$23
☐	91404	Clinical Trials: Considerations for Women and Ethnic Minorities/5	$43

Full Course Availability List *(Cont'd)*

✓	Course #	Course Title/Credits	Price

MEDICAL / SURGICAL

☐	40944	Acute Coronary Syndrome/15	$113
☐	40953	Moderate Sedation/5	$43
☐	90073	Migraine: Diagnosis and Therapeutic Advances/5	$43
☐	90120	Pulmonary Embolism/2	$23
☐	90180	Agitation, Sedation, and Delirium in Adult ICU Patients/5	$43
☐	90201	Botulinum Toxin and Dermal Fillers for Facial Aging/10	$78
☐	90214	Diagnosing and Managing Headaches/10	$78
☐	90241	Pancreatic Cancer/10	$78
☐	90284	Ischemic Stroke/10	$78
☐	90374	Clinical Management of Ventricular Arrhythmias/15	$113
☐	90424	Seizures and Epilepsy Syndromes/10	$78
☐	90444	A Review of Interventional Radiology/10	$78
☐	90471	Safe Clinical Use of Fluoroscopy/10	$78
☐	90484	Asthma: Diagnosis and Management/10	$78
☐	90564	Disorders and Injuries of the Eye and Eyelid/15	$113
☐	90683	Oral Cancer and Complications of Cancer Therapies/5	$43
☐	90744	Transport Methods for Critically Ill Patients/15	$113
☐	90773	Skin Cancers/5	$43
☐	90782	Colorectal Cancer/15	$113
☐	90804	Antibradycardia Pacemakers/15	$113
☐	90824	Clinical Management of Atrial Fibrillation/10	$78
☐	90844	Hyperlipidemias & Atherosclerotic Cardiovascular Disease/10	$78
☐	90984	Bariatric Surgery for Weight Loss/5	$43

MEN'S HEALTH

☐	93764	Men's Health Issues/15	$113
☐	93772	Male Sexual Dysfunction/10	$78
☐	93884	Prostate Cancer/5	$43

PEDIATRICS

☐	92074	Care of the Pediatric Trauma Patient/15	$113
☐	92204	Autism Spectrum Disorder/5	$43
☐	92344	Childhood Leukemias and Lymphomas/15	$113
☐	92404	Pediatric Abusive Head Trauma/1.5	$23

PHARMACOLOGY

☐	45122	Strategies for Appropriate Opioid Prescribing: The Florida Req/5	$43
☐	95001	Expanding the Options: The Drug-Approval Process in the U.S./5	$43
☐	95010	Managing Drug Interactions with Direct Oral Anticoagulants/1	$23
☐	95074	Antibiotics Review/5	$43
☐	95082	Antidepressant-Associated Sexual Dysfunction/1	$23
☐	95103	An Introduction to Pharmacogenetic Testing/1	$23
☐	95131	Prescription Opioids & Pain Mgmt: The Tennessee Guidelines/2	$23
☐	95142	Optimizing Opioid Safety and Efficacy/15	$113
☐	95152	Responsible and Effective Opioid Prescribing/3	$29
☐	95173	Medical Marijuana and Other Cannabinoids/5	$43
☐	95211	Responsible Prescribing of Controlled Substances: The LA Req/3	$29
☐	95300	Substance Use Disorders & Pain Mgmt: MATE Act Training/8	$77
☐	95500	Opioid Safety: Balancing Benefits and Risks/5	$43

✓	Course #	Course Title/Credits	Price

PSYCHIATRIC / MENTAL HEALTH

☐	96013	Post-Traumatic Stress Disorder/15	$113
☐	96103	Frontotemporal Degeneration/2	$23
☐	96154	Alzheimer's Disease/15	$113
☐	96182	Anxiety Disorders/15	$113
☐	96214	Attention Deficit Hyperactivity Disorder/5	$43
☐	96222	Borderline Personality Disorder/15	$113
☐	96313	Human Trafficking and Exploitation/5	$43
☐	96342	Mental Health Issues Common to Veterans & Their Families/2	$23
☐	96404	Depression and Suicide/15	$113
☐	96412	Behavioral Addictions/15	$113
☐	96424	Cyberbullying and Harassment/5	$43
☐	96431	Mass Shooters and Murderers: Motives and Paths/15	$113
☐	96442	Suicide Assessment and Prevention/6	$50
☐	96474	Obsessive-Compulsive Disorder/4	$36
☐	96564	Alcohol and Alcohol Use Disorders/10	$78
☐	96690	Anxiety Disorders in Older Adults/3	$29
☐	96790	Psychedelic Medicine and Interventional Psychiatry/10	$78
☐	96912	Novel Psychoactive Substances: Trends in Drug Abuse/5	$43
☐	96944	Cocaine Use Disorder/5	$43
☐	96954	Methamphetamine Use Disorder/5	$43
☐	96964	Opioid Use Disorder/10	$78
☐	96974	Cannabis and Cannabis Use Disorders/5	$43
☐	96984	Hallucinogens/4	$36
☐	96993	Club Drugs/3	$29

WOMEN'S HEALTH - MATERNAL / CHILD

☐	93010	Maternal Health Disparities/4	$36
☐	93032	Female Sexual Dysfunction/5	$43
☐	93113	Contraception/5	$43
☐	93253	Bleeding During Pregnancy/10	$78
☐	93504	Meanings of Menopause: Cultural Considerations/5	$43
☐	93604	Vaginal and Uterine Bleeding/5	$43

Please transfer your selected courses to the Additional Course Order Form on the envelope insert located between pages 60–61.

Selected Course Availability List

These courses may be ordered by mail on the Customer Information form located between pages 60–61.
We encourage you to **GO GREEN**. Access your courses **online** to save paper and **receive a discount**!
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MODERATE SEDATION
#40953 • 5 Credits
Book By Mail – $43 • ONLINE – $35
Mandate: VA
Purpose: The purpose of the course is to provide physicians with the information necessary to perform moderate sedation safely and according to existing guidelines in order to facilitate better patient care.
Audience: This course is designed for physicians in a variety of settings, including private practice, emergency department, radiology department, cardiac catheterization lab, and ambulatory surgery centers. The course is also of benefit to private practice physicians in family medicine and virtually all specialty areas.
Additional Approvals: ABIM, ABS, ABA, ABP
Special Approvals: This course meets the Virginia requirement for 4 hours of anesthesia education.

PROFESSIONAL BOUNDARIES AND SEXUAL MISCONDUCT IN MEDICINE
#41170 • 3 Credits
Book By Mail – $29 • ONLINE – $21
Mandate: GA
Purpose: The purpose of this course is to provide physicians and physician assistants with the knowledge and skills necessary to ethically and appropriately avoid boundary violations.
Audience: This course is designed for all physicians and physician assistants in all practice settings.
Additional Approvals: ABIM, ABS, ABA, ABP, ABPath
Special Approvals: This course meets the Georgia requirement for 2 hours of professional boundaries and sexual misconduct education.

MEDICAL ETHICS FOR PHYSICIANS
#47174 • 5 Credits
Book By Mail – $43 • ONLINE – $35
Mandate: CT, MA, MI, NV, PA, RI, TX
Purpose: The purpose of this course is to briefly review the history, theory, and practical application of ethical principles to issues that arise in clinical practice. The goals of the course are to heighten awareness and promote self-reflection, address knowledge gaps, improve communication and decision-making skills, and promote reasonable, humane care for patients and families.
Audience: This course is designed for physicians and interested healthcare professionals.
Additional Approvals: ABIM, ABS, ABA, ABP, ABPath
Special Approvals: This course meets the Michigan, Nevada, and Texas requirements for ethics/professional responsibility education and meets the Connecticut, Massachusetts, Pennsylvania, and Rhode Island requirements for risk management education.

PULMONARY EMBOLISM
NEW!
#90120 • 2 Credits
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: ABIM, ABS, ABA, ABPath

ISCHEMIC STROKE
UPDATE
#90284 • 10 Credits
Book By Mail – $78 • ONLINE – $70
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: ABIM, ABS, ABA

SAFE CLINICAL USE OF FLUOROSCOPY
#90471 • 10 Credits
By Mail – $78 • ONLINE – $70
Mandate: CA, MA (PAs)
Purpose: The purpose of this course is to provide healthcare providers with an understanding of the challenges encountered when using fluoroscopy in clinical practice and the tenets of safe fluoroscopy use in clinical practice.
Audience: This course is designed for physicians, nurses, radiology technicians, surgical technicians, and all healthcare staff involved in ensuring safe clinical use of fluoroscopy.
Additional Approvals: ABIM, ABS, ABA, ABP
Special Approvals: This course meets the California requirement for 4 hours of education in radiation safety for the clinical uses of fluoroscopy and 10 hours of education on the application of x-ray to the human body. This course meets the Massachusetts physician assistant requirement for 4 hours of fluoroscopic imaging education.

Selected Course Availability List *(Cont'd)*

PRESCRIBING OPIOIDS, PROVIDING NALOXONE, AND PREVENTING DRUG DIVERSION: THE WEST VIRGINIA REQUIREMENT

#91603 • 3 Credits

Book By Mail – $29 • ONLINE – $21

Mandate: WV

Purpose: The purpose of this course is to provide clinicians who prescribe or distribute opioids with an appreciation for the complexities of opioid prescribing and the dual risks of litigation due to inadequate pain control and drug diversion or misuse in order to provide the best possible patient care and to prevent a growing social problem.
Audience: This course is designed for all physicians, physician assistants, and nurses in West Virginia who may alter prescribing practices or intervene to prevent drug diversion and inappropriate opioid use.
Additional Approvals: ABIM, ABS, ABA
Special Approvals: This program has been approved by the WV Board of Medicine and will satisfy the required 3 hours of CME for Drug Diversion Training and Best Practice Prescribing of Controlled Substances Training for MDs and their licensed Physician Assistants.

MATERNAL HEALTH DISPARITIES

#93010 • 4 Credits

Book By Mail – $36 • ONLINE – $28

Mandate: IL, NJ

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: ABIM, ABS, ABP
Special Approvals: This course meets the New Jersey requirement for 1 hour of implicit and explicit bias education for those who provide perinatal care and treatment to pregnant persons and 4 hours of cultural competency education. This course meets the Illinois requirement for 1 hour of cultural competency education.

PRESCRIPTION OPIOIDS AND PAIN MANAGEMENT: THE TENNESSEE GUIDELINES

#95131 • 2 Credits

By Mail – $23 • ONLINE – $15

Mandate: TN

Purpose: The purpose of this course is to provide clinicians who prescribe or distribute opioids with clinical guidance for management of chronic pain and opioid prescription drug use that conforms with Tennessee Department of Health guidelines and with clinical tools designed to assess the risk of drug-seeking and diverting behaviors. The goal is to promote best practice patient care and prevent the growing public health problem of drug misuse, diversion, and overdose.
Audience: This course is designed for all clinicians who may alter prescribing practices or intervene to prevent drug diversion and inappropriate opioid use.
Additional Approvals: ABIM, ABS, ABA, ABP
Special Approvals: This course is designed to meet the Tennessee requirement for 2 hours of education on the prescribing of controlled substances, including instruction in the Tennessee Chronic Pain Guidelines.

SUBSTANCE USE DISORDERS AND PAIN MANAGEMENT: MATE ACT TRAINING

#95300 • 8 Credits

Book By Mail – $64 • ONLINE – $56

Mandate: Federal, Multi-State

Purpose: The purpose of this course is to provide clinicians who prescribe or distribute controlled substances with an appreciation for the complexities of managing patients with substance use disorders and comorbid pain in order to provide the best possible patient care and to prevent a growing social problem.
Audience: This course is designed for all healthcare professionals who may alter prescribing practices or intervene to help meet the needs of patients with substance use disorders.
Additional Approvals: ABIM, ABS, ABA, ABP, ABPath
Special Approvals: This course meets state and federal requirements for opioid/controlled substance, pain management, and addiction education.

HUMAN TRAFFICKING AND EXPLOITATION

#96313 • 5 Credits

Book By Mail – $43 • ONLINE – $35

Mandate: MI, VA

Purpose: As human trafficking becomes an increasingly more common problem in the United States, healthcare and mental health professionals will require knowledge of human trafficking patterns, the health and mental health needs of human trafficking victims, and successful interventions for victims. The purpose of this course is to increase the level of awareness and knowledge about human trafficking and exploitation so health and mental health professionals can identify and intervene in cases of exploitation.
Audience: This course is designed for physicians, nurses, social workers, pharmacy professionals, therapists, mental health counselors, and other members of the interdisciplinary team who may intervene in suspected cases of human trafficking and/or exploitation.
Additional Approvals: ABIM, ABP, ABPath
Special Approvals: This course meets the Michigan one-time and Virginia requirements for human trafficking education.

SUICIDE ASSESSMENT AND PREVENTION

#96442 • 6 Credits

By Mail – $50 • ONLINE – $42

Mandate: CT, NV, TX, WA

Purpose: The purpose of this course is to provide health and mental health professionals with an appreciation of the impact of depression and suicide on patient health as well as the skills necessary to identify and intervene for patients at risk for suicide.
Audience: This course is designed for healthcare professionals who may identify persons at risk for suicide and intervene to prevent or manage suicidality.
Additional Approvals: ABIM, ABS, ABP
Special Approvals: This course meets the Connecticut requirement for 2 hours of behavioral health education. This course is approved by the Nevada State Board of Medical Examiners to fulfill 2 hours of Suicide Prevention and Awareness education. This course meets the Texas requirement for medical ethics/professional responsibility education. This course is approved by the State of Washington Department of Health to fulfill the requirement for Suicide Prevention training for healthcare professionals. Approval number TRNG.TG.60715375-SUIC.

Selected Course Availability List *(Cont'd)*

CANNABIS AND CANNABIS USE DISORDERS

#96974 • 5 Credits

Book By Mail – $43 • ONLINE – $35

Mandate: NM, OR

Purpose: The purpose of this course is to allow healthcare professionals to effectively identify, diagnose, treat, and provide appropriate referrals for patients with cannabis use disorders.

Audience: This course is designed for health and mental health professionals who are involved in the evaluation or treatment of persons who use cannabis, either illicitly or as an adjunct to medical treatment.

Additional Approvals: ABIM, ABS, ABP

Special Approvals: This course meets the New Mexico requirement for 2 hours of cannabis education and the Oregon requirement for 3 hours of medical marijuana education. This course meets 5 hours of addiction education.

IMPLICIT BIAS IN HEALTH CARE

#97001 • 3 Credits

Book By Mail – $29 • ONLINE – $21

Mandate: IL, MA

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

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

Additional Approvals: ABIM, ABS, ABA, ABP, ABPath

Special Approvals: This course meets the Illinois and Massachusetts requirements for implicit bias training.

SEXUAL ASSAULT

#97023 • 3 Credits

By Mail – $29 • ONLINE – $21

Mandate: CT, SC, TX

Purpose: The purpose of this course is to address knowledge gaps, enhance clinical examination and management skills, and improve treatment outcomes for victims of sexual assault.

Audience: This course is intended for physicians and other healthcare professionals who may be called upon to provide care to victims of sexual assault.

Additional Approvals: ABIM, ABS, ABP, ABPath

Special Approvals: This course meets the Connecticut requirement for sexual assault education, the South Carolina requirement for encouraged education in domestic violence, and the Texas requirement for forensic evidence education for those who perform examinations on sexual assault survivors.

SEXUAL HARASSMENT PREVENTION: THE ILLINOIS REQUIREMENT

#97081 • 1 Credit

By Mail – $23 • ONLINE – $15

Mandate: IL

Purpose: The purpose of this course is to provide health and mental health professionals with clear knowledge of the consequences of sexual harassment and the skills to help combat harassment in the workplace.

Audience: This course is designed for members of the interprofessional healthcare team who may act to prevent sexual harassment.

Additional Approvals: ABIM, ABS, ABA, ABP

Special Approvals: This course is designed to fulfill the Illinois requirement for sexual harassment education.

PALLIATIVE CARE AND PAIN MANAGEMENT AT THE END OF LIFE

#97384 • 15 Credits

Book By Mail – $113 • ONLINE – $105

Mandate: CA, IA, MA, NJ, VT

Purpose: The purpose of this course is to bridge the gap in knowledge of palliative care by providing an overview of the concept of palliative care and a discussion of the benefits and barriers to optimum palliative care at the end of life.

Audience: This course is designed for all members of the interdisciplinary team, including physicians, physician assistants, nurse practitioners, nurses, social workers, marriage and family therapists, and other members seeking to enhance their knowledge of palliative care.

Additional Approvals: ABIM, ABS, ABA

Special Approvals: This course fulfills 11 hours of education on the appropriate care of the terminally ill for California-licensed physicians who must complete 12 hours of pain management and the appropriate care of the terminally ill. This course meets the Iowa, Massachusetts, New Jersey, and Vermont requirements for end-of-life education.

IMPLICIT BIAS: THE MICHIGAN REQUIREMENT

#97440 • 2 Credits

ONLINE ONLY – $30

Mandate: MI

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

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

Additional Approvals: ABIM, ABS, ABA, ABP, ABPath

Special Approvals: This course meets 2 of the 3 hours of implicit bias education required for physicians and 2 hours required for physician assistants.

ADDRESSING IMPLICIT BIAS TO IMPROVE PATIENT CARE

#24-689 • 1 Credit

WEBINAR – $15

Mandate: MI

Purpose: The purpose of this webinar is to define and explore implicit and explicit bias and to provide healthcare professionals with the knowledge and skills necessary to prevent implicit bias from negatively impacting patient care.

Audience: This course is designed for members of the interprofessional healthcare team who may intervene to identify and address implicit bias.

Additional Approvals: ABIM, ABS, ABA, ABP, ABPath

Special Approvals: This course meets 1 of the 3 hours of implicit bias education required for physicians and 1 hours required for physician assistants.

Selected Course Availability List *(Cont'd)*

HUMAN TRAFFICKING AND EXPLOITATION: THE TEXAS REQUIREMENT

#97471 • 5 Credits

By Mail – $43 • ONLINE – $35

Mandate: TX

NEW!

Purpose: The purpose of this course is to increase the level of awareness and knowledge about human trafficking and exploitation so health and mental health professionals can identify and intervene in cases of exploitation.

Audience: This course is designed for Texas physicians, nurses, social workers, pharmacy professionals, therapists, mental health counselors, and other members of the interdisciplinary team who may intervene in suspected cases of human trafficking and/or exploitation.

Additional Approvals: ABIM, ABS, ABA, ABP

Special Approvals: This course has been approved by the Texas Health and Human Services Commission (HHSC) to meet the requirement for human trafficking training.

CHILD ABUSE IDENTIFICATION AND REPORTING: AN UPDATE FOR NEW YORK

#97534 • 2 Credits

By Mail – $23 • ONLINE – $15

Mandate: NY

Required Update

Purpose: The purpose of this course is to enable healthcare professionals in all practice settings to define child abuse and identify the children who are affected by violence. This course describes how a victim can be accurately diagnosed and identifies the community resources available in the state of New York for child abuse victims.

Audience: This course is designed for all New York physicians, physician assistants, nurses, and other professionals required to complete child abuse education.

Additional Approvals: ABIM, ABS, ABP, ABPath

Special Approvals: This course is approved by the New York State Education Department to fulfill the updated requirement for 2 hours of training in the Identification and Reporting of Child Abuse and Maltreatment. Provider #80673.

INFECTION CONTROL: THE NEW YORK REQUIREMENT

#98643 • 5 Credits

By Mail – $43 • ONLINE – $35

Mandate: NY

Purpose: The purpose of this course is to provide a review of current infection control practices and accepted standards, with an emphasis on the application of infection control standards and practices in outpatient and ambulatory settings.

Audience: This course is designed for physicians, physician assistants, nurses, and other healthcare professionals in New York required to complete education to enhance their knowledge of infection control.

Additional Approvals: ABIM, ABS, ABA, ABP, ABPath

Special Approvals: This course is approved by the New York State Department of Health to fulfill the requirement for 4 hours of Infection Control Training as mandated by Chapter 786 of the Laws of 1992. Provider #OT10781.

All Faculty and Division Planners have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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

ALZHEIMER DISEASE AND DEMENTIAS: EARLY DETECTION AND CARE PLANNING

#99090 • 3 Credits

Book By Mail – $29 • ONLINE – $21

Mandate: CA, IL, MA

NEW!

Purpose: 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.

Audience: This course is designed for physicians, PAs, and nursing professionals who are involved in the care of patients who have or may develop dementia.

Additional Approvals: ABIM, ABS

Special Approvals: This course meets the Massachusetts requirement for cognitive impairment education and the Illinois requirement for 1 hour of Alzheimer's education. This course meets the California requirement for geriatrics education.

ABIM CME MOC ACCREDITED

Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit. Completion of a course constitutes permission to share the completion data with ACCME.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the learner to earn credit toward the CME and Self-Assessment requirements of the American Board of Surgery's Continuous Certification program. It is the CME activity provider's responsibility to submit learner completion information to ACCME for the purpose of granting ABS credit.

PART 2 MOC THE AMERICAN BOARD of PEDIATRICS

Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity in the American Board of Pediatrics' (ABP) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABP MOC credit.

MOCA™

Designated activities contribute to the patient safety CME requirement for Part II: Lifelong Learning and Self-Assessment of the American Board of Anesthesiology's (ABA) redesigned Maintenance of Certification in Anesthesiology Program® (MOCA®), known as MOCA 2.0®. Please consult the ABA website, www.theABA.org, for a list of all MOCA 2.0 requirements.

Participants will earn CC points equivalent to the amount of CME credits claimed for the activity in the American Board of Pathology area of Lifelong Learning (Part II).

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- ☐ Email - FREE!
- ☐ Fax - FREE!
- ☐ Mail - Add $6 for shipping and handling

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☐	91660	Falls and Fall Prevention / 3 Credits	$21
☐	94820	Chronic Cough in Adults / 10 Credits	$70
☐	96404	Depression and Suicide / 15 Credits	$105

Additional Courses Available by Mail (ACCESS ONLINE FOR A DISCOUNT!)

Payment must accompany this form. To order by phone, please have your credit card ready.

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☐	41170	Prof. Boundaries & Sexual Misconduct in Medicine / 3	$29
☐	47174	Medical Ethics for Physicians / 5	$43
☐	90120	Pulmonary Embolism / 2	$23
☐	90284	Ischemic Stroke / 10	$78
☐	90471	Safe Clinical Use of Fluoroscopy / 10	$78
☐	91603	Prescribing Opioids: The WV Requirement / 3	$29
☐	93010	Maternal Health Disparities / 4	$36
☐	95131	Prescription Opioids & Pain Mgmt: TN Guidelines / 2	$23
☐	95300	Substance Use Disorders & Pain Mgmt: MATE Act / 8	$77
☐	96313	Human Trafficking and Exploitation / 5	$43
☐	96442	Suicide Assessment and Prevention / 6	$50
☐	96974	Cannabis and Cannabis Use Disorders / 5	$43
☐	97001	Implicit Bias in Health Care / 3	$29
☐	97023	Sexual Assault / 3	$29
☐	97081	Sexual Harassment Prevention: The IL Req. / 1	$23
☐	97384	Palliative Care and Pain Mgmt at the End of Life / 15	$113
☐	97440	Implicit Bias: The MI Requirement (Webinar) / 2	$30
☐	24-689	Addressing Implicit Bias to Improve Pt Care (Webinar) / 1	$15
☐	97471	Human Trafficking and Exploitation: The TX Req. / 5	$43
☐	97534	NY Child Abuse Identification and Reporting / 2	$23
☐	98643	Infection Control: The New York Requirement / 5	$43
☐	99090	Alzheimer Disease and Dementias / 3	$29

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Credit card #

Expiration date / Security code

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Grand Total

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Answer Sheet

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Please note the following:

- In accordance with the *AMA PRA Category 1 Credit™* system, physicians must complete and pass a post-test to receive credit.
- A passing grade of at least 70% must be achieved on each course test in order to receive credit.
- Darken only one circle per question.
- Use pen or pencil; please refrain from using markers.
- **Information on the Customer Information form must be completed**.
- **Include the completed and signed mandatory Evaluation**. Your postmark or facsimile date will be used as your completion date.

#95152 RESPONSIBLE AND EFFECTIVE OPIOID PRESCRIBING—3 CREDITS Please refer to pages 18–19.

Expiration Date: 04/30/27 *May be taken individually for $21*

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

#91660 FALLS AND FALL PREVENTION—3 CREDITS Please refer to page 30.

Expiration Date: 03/31/27 *May be taken individually for $21*

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

#94820 CHRONIC COUGH IN ADULTS—10 CREDITS Please refer to pages 63–65.

Expiration Date: 07/31/27 *May be taken individually for $70*

	A	B	C	D		A	B	C	D		A	B	C	D		A	B	C	D
1.	❍	❍	❍	❍	6.	❍	❍	❍	❍	11.	❍	❍	❍	❍	16.	❍	❍	❍	❍
2.	❍	❍	❍	❍	7.	❍	❍	❍	❍	12.	❍	❍	❍	❍	17.	❍	❍	❍	❍
3.	❍	❍	❍	❍	8.	❍	❍	❍	❍	13.	❍	❍	❍	❍	18.	❍	❍	❍	❍
4.	❍	❍	❍	❍	9.	❍	❍	❍	❍	14.	❍	❍	❍	❍	19.	❍	❍	❍	❍
5.	❍	❍	❍	❍	10.	❍	❍	❍	❍	15.	❍	❍	❍	❍	20.	❍	❍	❍	❍

#96404 DEPRESSION AND SUICIDE—15 CREDITS Please refer to pages 112–114.

Expiration Date: 07/31/26 *May be taken individually for $105*

	A	B	C	D		A	B	C	D		A	B	C	D
1.	❍	❍	❍	❍	11.	❍	❍	❍	❍	21.	❍	❍	❍	❍
2.	❍	❍	❍	❍	12.	❍	❍	❍	❍	22.	❍	❍	❍	❍
3.	❍	❍	❍	❍	13.	❍	❍	❍	❍	23.	❍	❍	❍	❍
4.	❍	❍	❍	❍	14.	❍	❍	❍	❍	24.	❍	❍	❍	❍
5.	❍	❍	❍	❍	15.	❍	❍	❍	❍	25.	❍	❍	❍	❍
6.	❍	❍	❍	❍	16.	❍	❍	❍	❍					
7.	❍	❍	❍	❍	17.	❍	❍	❍	❍					
8.	❍	❍	❍	❍	18.	❍	❍	❍	❍					
9.	❍	❍	❍	❍	19.	❍	❍	❍	❍					
10.	❍	❍	❍	❍	20.	❍	❍	❍	❍					

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Evaluation

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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, including the questions?
   (Physicians should only claim credit commensurate with the extent of their participation in the 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 this course, did you identify the necessity for education on the topic to improve your professional 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 evidence-based practice recommendations assist in determining the validity or relevance of the information?
11. Are you more confident in your ability to provide patient care after completing this course?
12. Do you plan to make changes in your practice as a result of this course content?
13. May we contact you later regarding planned changes in your practice and changes in treatment or health status of your patients as a result of this activity?

#95152 3 Credits	#91660 3 Credits	#94820 10 Credits	#96404 15 Credits
1. ☐ New ☐ Review	1. ☐ New ☐ Review	1. ☐ New ☐ Review	1. ☐ New ☐ Review
2. _____ Hours	2. _____ Hours	2. _____ Hours	2. _____ Hours
3. ☐ Yes ☐ No	3. ☐ Yes ☐ No	3. ☐ Yes ☐ No	3. ☐ Yes ☐ No
4. ☐ Yes ☐ No	4. ☐ Yes ☐ No	4. ☐ Yes ☐ No	4. ☐ Yes ☐ No
5. ☐ Yes ☐ No	5. ☐ Yes ☐ No	5. ☐ Yes ☐ No	5. ☐ Yes ☐ No
6. ☐ Yes ☐ No	6. ☐ Yes ☐ No	6. ☐ Yes ☐ No	6. ☐ Yes ☐ No
7. ☐ Yes ☐ No	7. ☐ Yes ☐ No	7. ☐ Yes ☐ No	7. ☐ Yes ☐ No
8. ☐ Yes ☐ No	8. ☐ Yes ☐ No	8. ☐ Yes ☐ No	8. ☐ Yes ☐ No
9. ☐ Yes ☐ No	9. ☐ Yes ☐ No	9. ☐ Yes ☐ No	9. ☐ Yes ☐ No
10. ☒ N/A	10. ☒ N/A	10. ☒ N/A	10. ☒ N/A
11. ☐ Yes ☐ No	11. ☐ Yes ☐ No	11. ☐ Yes ☐ No	11. ☐ Yes ☐ No
12. ☐ Yes ☐ No	12. ☐ Yes ☐ No	12. ☐ Yes ☐ No	12. ☐ Yes ☐ No
13. ☐ Yes ☐ No	13. ☐ Yes ☐ No	13. ☐ Yes ☐ No	13. ☐ Yes ☐ No

#95152 Responsible and Effective Opioid Prescribing — If you answered YES to question #12, how specifically will this activity enhance your role as a member of the interdisciplinary team? _____

_____

#91660 Falls and Fall Prevention — If you answered YES to question #12, how specifically will this activity enhance your role as a member of the interdisciplinary team? _____

_____

#98420 Chronic Cough in Adults — If you answered YES to question #12, how specifically will this activity enhance your role as a member of the interdisciplinary team? _____

_____

#96404 Depression and Suicide — If you answered YES to question #12, how specifically will this activity enhance your role as a member of the interdisciplinary team? _____

_____

Signature _____

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Sub Total $			**Sub Total $**			**Sub Total $**		
						Total Price $		

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