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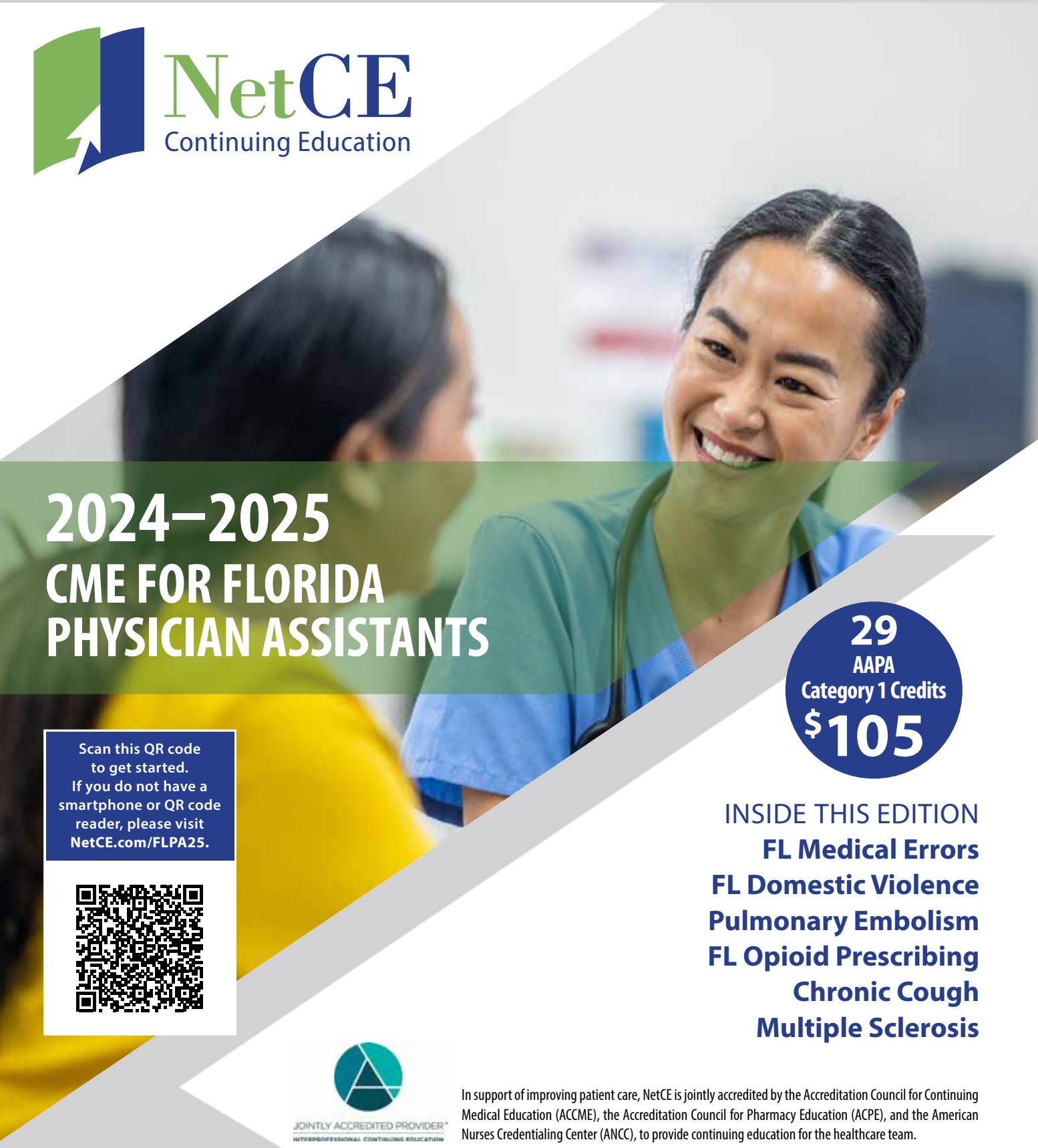

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2024–2025

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Medical Error Prevention and Root Cause Analysis

This course meets the Florida requirement for 2 hours of education on the Prevention of Medical Errors.

Audience
This course is designed for all licensed healthcare professionals.

Course Objective
The purpose of this course is to satisfy the requirement of the Florida law and provide all licensed healthcare professionals with information regarding the root cause process, error reduction and prevention, and patient safety.

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

1. Describe how the Institute of Medicine defines "medical error."
2. Describe the types of sentinel events the Joint Commission has identified.
3. Discuss what factors must be included in a root cause analysis in order for the Joint Commission to consider it "thorough" and "credible."
4. Identify what types of adverse incidents must be reported to the Florida Agency for Healthcare Administration.
5. Identify the most common sentinel events reported to the Joint Commission.
6. Evaluate the most common misdiagnoses, as recognized by the Florida Board of Medicine, and outline the safety needs of special populations, including non-English-proficient patients.

Faculty
Marjorie Conner Allen, BSN, JD, received her Bachelor of Science in Nursing degree from the University of Florida, Gainesville, in 1984. She began her nursing career at Shands Teaching Hospital and Clinics at the University of Florida, Gainesville. While practicing nursing at Shands, she gave continuing education seminars regarding the nursing implications for dealing with adolescents with terminal illness. In 1988, Ms. Allen moved to Atlanta, Georgia where she worked at Egleston Children's Hospital at Emory University in the bone marrow transplant unit. In the fall of 1989, she began law school at Florida State University. After graduating from law school in 1992, Ms. Allen took a two-year job as law clerk to the Honorable William Terrell Hodges, United States District Judge for the Middle District of Florida. After completing her clerkship, Ms. Allen began her employment with the law firm of Smith, Hulsey & Busey in Jacksonville, Florida where she has worked in the litigation department defending hospitals and nurses in medical malpractice actions. Ms. Allen resides in Jacksonville and is currently in-house counsel to the Mayo Clinic Jacksonville.

Faculty Disclosure

Contributing faculty, Marjorie Conner Allen, BSN, JD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Division Planner/Director Disclosure

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

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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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Through the American Board of Medical Specialties ("ABMS") ongoing commitment to increase access to practice relevant Continuing Certification Activities through the ABMS Continuing Certification Directory, Medical Error Prevention and Root Cause Analysis has met the requirements as a Lifelong Learning CME Activity (apply toward general CME requirement) for the following ABMS Member Boards: Allergy and Immunology; Anesthesiology; Colon and Rectal Surgery; Family Medicine; Medical Genetics and Genomics; Nuclear Medicine; Ophthalmology; Physical Medicine and Rehabilitation; Plastic Surgery; Preventive Medicine; Psychiatry and Neurology; Radiology; Thoracic Surgery; Urology.

Special Approvals

This course fulfills the Florida requirement for 2 hours of education on the Prevention of Medical Errors.

About the Sponsor

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

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INTRODUCTION

The Institute of Medicine's (IOM) 1999 publication *To Err is Human: Building a Safer Health System*, illuminated the unfortunate reality of medical errors in the healthcare industry. The report reviewed the prevalence of medical errors in the United States and highlighted measures that should be taken to prevent them. Specifically, the authors of the report noted that at least 44,000 and perhaps as many as 98,000 Americans were dying in hospitals each year as a result of medical errors and many more were being seriously injured [1]. They further noted that, even when using the lower estimate of 44,000, deaths in hospitals due to medical errors exceeded the annual deaths attributable to motor vehicle accidents (43,458), breast cancer (42,297), or AIDS (16,516) [1]. A 2016 report stated that the average number of annual in-hospital deaths attributable to medical error might actually be much higher, at around 400,000 [2]. This report places medical errors as the third leading cause of death in the United States. Certainly, these numbers must be balanced against the millions of admissions to hospitals in the United States, which is in excess of 33 million annually [1; 3].

It does appear that some progress has been made in the past decade. The Agency for Healthcare Research and Quality found a 17% decline in hospital-acquired conditions between 2014 and 2017, or 910,000 fewer conditions and 20,500 fewer deaths than if the 2014 rate had remained steady [4]. Though the precise mechanism(s) responsible for this decline is not clear, it occurred following a concerted effort by federal agencies, organizations, and individual providers to curtail medical errors. However, the statistics indicate that medical errors continue to be an issue. Healthcare professionals should commit to continuing to pay greater attention to evaluating approaches for reducing errors and to building new systems to reduce the incidence of medical errors.

Spurred by a commitment to reducing medical error incidents, the Florida Legislature mandates that all healthcare professionals in Florida complete a two-hour course on the topic of prevention of medical errors [5]. This continuing education course is designed to satisfy the requirements of the Florida law and provide all licensed healthcare professionals with information regarding the root cause analysis process, error reduction and prevention, and patient safety, as well as information regarding the five most misdiagnosed conditions as determined by the Florida Board of Medicine.

DEFINING "MEDICAL ERROR"

The IOM Committee on Quality of Healthcare in America defines error as "the failure of a planned action to be completed as intended or the use of a wrong plan to achieve an aim" [1]. It is important to note that medical errors are not defined as intentional acts of wrongdoing and that not all medical errors rise to the level of medical malpractice or negligence. Errors depend on two kinds of failures: either the correct action does not proceed as intended, which is described as an "error of execution," or the original intended action is not correct, which is described as an "error of planning" [1]. A medical error can occur at any stage in the process of providing patient care, from diagnosis to treatment, and even while providing preventative care. Not all errors will result in harm to the patient. Medical errors that do result in injury are sometimes called preventable adverse events or sentinel events—sentinel because they signal the need for immediate investigation and response [6].

Preventable adverse events or sentinel events are defined as those events that cause an injury to a patient as a result of medical intervention or inaction on the part of the healthcare provider whereby the injury cannot reasonably be said to be related to the patient's underlying medical condition. Thus, for example, if a patient has a surgical procedure and dies postoperatively from pneumonia, the patient has suffered an adverse event. But was that adverse event preventable; was it caused by medical intervention or inaction? The specific facts of this case must be analyzed to determine whether the patient acquired the pneumonia as a result of poor handwashing techniques of the medical staff (i.e., an error of execution), which would indicate a preventable adverse event, or whether the patient acquired the pneumonia because of age and comorbidities, which would indicate a nonpreventable adverse event.

Healthcare professionals can learn much by closely scrutinizing and evaluating adverse events that lead to serious injury or death. The evaluation of such events would also enable healthcare professionals to improve the delivery of health care and reduce future mistakes. In addition, healthcare professionals should have a process in place to evaluate those instances in which a medical error occurred and did not cause harm to the patient. By reviewing these processes, healthcare professionals are afforded the unique opportunity to identify system improvements that have the potential to prevent future adverse

events. The Joint Commission, recognizing the importance of analyzing both preventable adverse events and near-misses, has established guidelines for recognizing these events and requires healthcare facilities to conduct a root cause analysis to determine the underlying cause of the event [7].

ROOT CAUSE ANALYSIS PROCESS

The Joint Commission is a national organization with a mission to improve the quality of care provided at healthcare institutions in the United States. It accomplishes this mission by providing accredited status to healthcare facilities. Accreditors play an important role in encouraging and supporting actions within healthcare organizations by holding them accountable for ensuring a safe environment for patients. Healthcare organizations should actively engage in a cooperative relationship with the Joint Commission through this accreditation process and participate in the process to reduce risk and facilitate desired outcomes of care.

Root cause analysis, as defined by the Joint Commission, is "a process for identifying the basic or causal factors that underlie variation in performance, including the occurrence or possible occurrence of a sentinel event" [6]. In the 2022 update, the Joint Commission defines a sentinel event as a "patient safety event (not primarily related to the natural course of the illness or underlying condition) that reaches a patient and results in death, severe harm (regardless of duration of harm), or permanent harm (regardless of severity of harm)" [6; 10]. Furthermore, the Joint Commission revision clarified the terms "severe" and "permanent" harm with regard to sentinel events. "Severe harm" is an event or condition that reaches the individual, resulting in life-threatening bodily injury (including pain or disfigurement) that interferes with or results in loss of functional ability or quality of life that requires continuous physiologic monitoring or a surgery, invasive procedure, or treatment to resolve the condition [6; 10]."Permanent harm" is an event or condition that reaches the individual, resulting in any level of harm that permanently alters and/or affects an individual's baseline [6; 10].

The following subsets of sentinel events are subject to review by the Joint Commission [6; 11]:

- The event has resulted in an unanticipated death or major permanent loss of function, not related to the natural course of the patient's illness or underlying condition

or

- The event is one of the following (even if the outcome was not death or major permanent loss of function unrelated to the natural course of the patient's illness or underlying condition):
  - Suicide of any patient receiving care, treatment, and services in a staffed around-the-clock care setting or within 72 hours of discharge
  - Unanticipated death of a full-term infant
  - Abduction of any patient receiving care, treatment, and services
  - Any elopement (i.e., unauthorized departure) of a patient from a staffed around the-clock care setting (including the emergency department), leading to death, permanent harm, or severe temporary harm to the patient
  - Discharge of an infant to the wrong family
  - Rape, assault (leading to death or permanent loss of function), or homicide of any patient receiving care, treatment, and services
  - Rape, assault (leading to death or permanent loss of function), or homicide of a staff member, licensed independent practitioner, visitor, or vendor while on site at the healthcare organization
  - Hemolytic transfusion reaction involving administration of blood or blood products having major blood group incompatibilities (e.g., ABO, Rh, other blood groups)
  - Invasive procedure, including surgery, on the wrong patient or wrong site
  - Unintended retention of a foreign object in a patient after surgery or other invasive procedures
  - Severe neonatal hyperbilirubinemia (bilirubin >30 mg/dL)
  - Fluoroscopy resulting in permanent tissue injury when clinical and technical optimization were not implemented and/or recognized practice parameters were not followed
  - Fire, flame, or unanticipated smoke, heat, or flashes occurring during an episode of patient care
  - Any intrapartum (related to the birth process) maternal death
  - Severe maternal morbidity
  - Fall resulting in: any fracture; surgery, casting, or traction; required consult/management or comfort care for a neurological or internal injury; a patient with coagulopathy who receives blood products as a result of the fall; or death or permanent harm as a result of injuries sustained from the fall (not from physiologic events causing the fall)

Alternatively, the following examples are events that are NOT considered reviewable under the Joint Commission's sentinel event policy [6]:

- Any close call ("near miss")

- Full or expected return of limb or bodily function to the same level as prior to the adverse event by discharge or within two weeks of the initial loss of said function, whichever is the longer period
- Any sentinel event that has not affected a recipient of care (e.g., patient, individual, resident)
- Medication errors that do not result in death or major permanent loss of function
- Suicide other than in an around-the-clock care setting or following elopement from such a setting
- A death or loss of function following a discharge against medical advice
- Unsuccessful suicide attempts unless resulting in major permanent loss of function
- Minor degrees of hemolysis not caused by a major blood group incompatibility and with no clinical sequelae

For further definition of terms, please refer to the Joint Commission's Sentinel Event Policy and Procedures at https://www.jointcommission.org/resources/patient-safety-topics/sentinel-event/sentinel-event-policy-and-procedures.

As part of the accreditation requirement, the Joint Commission requires that healthcare organizations have a process in place to recognize these sentinel events, conduct thorough and credible root cause analyses that focus on process and system factors, and document a risk-reduction strategy and internal corrective action plan that includes measurement of the effectiveness of process and system improvements to reduce risk [6]. This process must be completed within 45 business days of the organization having become aware of the sentinel event.

The Joint Commission will consider a root cause analysis acceptable for accreditation purposes if it focuses primarily on systems and processes, not individual performance [6]. In other words, the healthcare organization should minimize the individual blame or retribution for involvement in a medical error. In addition, the root cause analysis should progress from special causes in clinical processes to common causes in organizational processes, and the analysis should repeatedly dig deeper by asking why, then, when answered, why again, and so on. The analysis should also identify changes that can be made in systems and processes, either through redesign or development of new systems or processes, which would reduce the risk of such events occurring in the future. The Joint Commission requires that the analysis be thorough and credible. To be considered thorough, the root cause analysis must include [6]:

- A determination of the human and other factors most directly associated with the sentinel event and the process(es) and systems related to its occurrence
- Analysis of the underlying systems and processes through a series of "why" questions to determine where redesign might reduce risk
- Inquiry into all areas appropriate to the specific type of event
- Identification of risk points and their potential contributions to this type of event
- A determination of potential improvement in processes or systems that would tend to decrease the likelihood of such events in the future, or a determination, after analysis, that no such improvement opportunities exist

To be considered credible, the root cause analysis must meet the following standards [6]:

- The organization's leadership and the individuals most closely involved in the process and systems under review must participate in the analysis.
- The analysis must be internally consistent; that is, it must not contradict itself or leave obvious questions unanswered.
- The analysis must provide an explanation for all findings of "not applicable" or "no problem."
- The analysis must include consideration of any relevant literature.

Finally, as previously discussed, after conducting this root cause analysis, the organization must prepare an internal corrective action plan. The Joint Commission will accept this action plan if it identifies changes that can be implemented to reduce risk or formulate a rationale for not undertaking such changes, and if, where improvement actions are planned, it identifies who is responsible for implementation, when the action will be implemented, and how the effectiveness of the actions will be evaluated [6].

FLORIDA LAW

Healthcare professionals have an obligation to report adverse events to leadership and ensure that organizations have processes in place to satisfy the Joint Commission requirement. In Florida, certain serious adverse incidents must also be reported to Florida's Agency for Health Care Administration (AHCA). Florida law requires that licensed facilities, such as hospitals, establish an internal risk management program. As part of that program, licensed facilities must develop and implement an incident reporting system, which requires the development of appropriate measures to minimize the risk of adverse incidents to patients, as well as imposes an affirmative duty on all healthcare providers and employees of the facility to report adverse incidents to the risk manager or to his or her designee. The risk manager must receive these incident reports within 3 business days of the incident, and depending on the type of incident, the risk manager may have to report the incident to AHCA within 15 days of receipt of the report.

Florida Statute 395.0197 specifically defines an adverse incident as [8]:

For purposes of reporting to the agency pursuant to this section, the term "adverse incident" means an event over which health care personnel could exercise control and which is associated in whole or in part with medical intervention, rather than the condition for which such intervention occurred, and which:

a) Results in one of the following injuries:
   1. Death;
   2. Brain or spinal damage;
   3. Permanent disfigurement;
   4. Fracture or dislocation of bones or joints;
   5. A resulting limitation of neurological, physical, or sensory function which continues after discharge from the facility;
   6. Any condition that required specialized medical attention or surgical intervention resulting from nonemergency medical intervention, other than an emergency medical condition, to which the patient has not given his or her informed consent; or
   7. Any condition that required the transfer of the patient, within or outside the facility, to a unit providing a more acute level of care due to the adverse incident, rather than the patient's condition prior to the adverse incident
b) Was the performance of a surgical procedure on the wrong patient, a wrong surgical procedure, a wrong-site surgical procedure, or a surgical procedure otherwise unrelated to the patient's diagnosis or medical condition;
c) Required the surgical repair of damage resulting to a patient from a planned surgical procedure, where the damage was not a recognized specific risk, as disclosed to the patient and documented through informed-consent process; or
d) Was a procedure to remove unplanned foreign objects remaining from a surgical procedure.

In 2021, the Florida AHCA reported that a total of 184 deaths occurred as a result of hospital error, 21.4% of 859 adverse incidents reported for the year. The next most common incidents during this period were transfer of the patient to a unit providing a more acute level of care due to the adverse incident (18.7%), fracture or dislocation of bones or joints (17.0%), surgical procedures unrelated to the patient's diagnosis or medical needs (10.4%), surgical procedure to remove foreign object from a previous surgical procedure (10.2%), brain or spinal damage (5.0%), and surgical procedure performed on wrong site (4.3%) [9]. The following adverse incidents must be reported to the AHCA within 15 calendar days after their occurrence [8]:

- The death of a patient
- Brain or spinal damage to a patient
- The performance of a surgical procedure on the wrong patient
- The performance of a wrong-site surgical procedure
- The performance of a wrong surgical procedure
- The performance of a surgical procedure that is medically unnecessary or otherwise unrelated to the patient's diagnosis or medical condition
- The surgical repair of damage resulting to a patient from a planned surgical procedure, where the damage is not a recognized specific risk, as disclosed to the patient and documented through the informed-consent process
- The performance of procedures to remove unplanned foreign objects remaining from a surgical procedure

Each incident will be reviewed by the AHCA, who will then determine the penalty to be imposed upon the responsible party [8]. All Florida healthcare professionals who practice in licensed facilities should familiarize themselves with these requirements and ensure that the facility in which they practice has processes in place to ensure compliance.

Unlike Florida's mandatory reporting of serious adverse incidents, the Joint Commission recommends that healthcare organizations voluntarily report sentinel events, and it encourages the facilities to communicate the results of their root cause analyses and their corrective action plans. As a result of the sentinel events that have been reported, the Joint Commission has compiled Sentinel Event Alerts. These alerts are intended to provide healthcare organizations with important information regarding reported trends and, by doing so, highlight areas of potential concern so an organization may review its own internal processes to maximize error reduction and prevention with regard to a particular issue [7].

ERROR REDUCTION AND PREVENTION

Between 2005 and 2021, the Joint Commission reviewed 14,731 sentinel events [11]. Some events, such as fire, impacted multiple patients. Sentinel event reviews during this time period were frequently conducted for patient fall; delay in treatment; unintended retention of a foreign body; wrong-patient, wrong-site, wrong-procedure surgery; patient suicide; operative and postoperative complications; and medication error [11].

PATIENT FALLS

In 2021, the Joint Commission introduced a separate sentinel event line item for patient falls, making it the most frequently reported sentinel event that year. Patients who are at highest risk include the elderly, those who have an altered mental status due to chronic mental illness or acute intoxication, and those who have a history of prior falls. Additionally, the Joint Commission calls for an increased awareness to an underrecognized population at risk for falls. Newborns and infants

are at risk for falls and/or drops, often due to maternal risk factors such as cesarean birth, use of pain medication within four hours, second or third postpartum night (specifically around midnight to early morning hours), and drowsiness associated with breastfeeding. It is obvious from these factors that a thorough and complete patient history may be the key to identifying those at risk.

The root causes of patient falls that healthcare facilities identified as sentinel events and reported to the Joint Commission included inadequate assessment; communication failures; lack of adherence to protocols and safety practices; inadequate staff orientation, supervision, staffing levels, or skill mix; deficiencies in the physical environment; and lack of leadership [19]. Risk reduction strategies to these root causes are fairly straightforward, although in practice, preventing falls is difficult. The most important are the use of a standardized assessment tool to identify fall and injury risk factors, assessing an individual patient's risks that may not have been captured through the tool, and interventions tailored to an individual patient's identified risks [19].

Because patient falls often result in morbidity, mortality, immobility, and early nursing home placement for patients, it is imperative that healthcare facilities initiate adequate fall prevention programs, which will ultimately reduce injuries. Failure to do so will result in a spiraling increase in the number of falls in healthcare facilities, particularly among the elderly who are at highest risk. As more Americans live beyond 65 years of age, the need to develop mobility protocols and programs to reduce the risk of falls and injuries for the older adult grows more urgent.

DELAYS IN TREATMENT

According to the Joint Commission, more than half of all reported delay in treatment sentinel events in 2010–2014 resulted in patient death [16]. It is important to keep in mind that delays in treatment can occur in any healthcare setting. The most common reason for a delay in treatment is misdiagnosis; however, delays can also result from delayed test results, lack of physician availability, delayed administration of ordered care, incomplete treatment, and even inability to get an initial appointment or follow-up appointment in a timely manner [16]. The main root causes contributing to delays in treatment are inadequate assessments, poor planning, communication failures, and human factors. Additionally, 48% of patients self-reported a delay in accessing healthcare during the COVID-19 pandemic. One study suggests that delays in treatment are likely due to widespread public health messages to avoid unnecessary visits, triage uncertainty, lack of providers, and lack of resources [36]. Recommendations from the Joint Commission include avoiding cognitive shortcuts, improving health information technology, incorporating diagnostic checklists into the electronic record, promoting provider-to-provider communication, engaging leadership in developing solutions, focusing organization attention on the scheduling process and on ordering tests and reporting test results, improving access to care, implementing a standardized communications method, maintaining adequate staffing levels, and increasing patient and family engagement/activation [16].

UNINTENDED RETENTION OF A FOREIGN BODY

In 2021, unintended retained foreign objects were the third most frequently reported sentinel event reported to the Joint Commission [11]. The prevalence of these events has remained relatively stable since 2009, indicating that preventing these errors remains difficult for practitioners and facilities. The most commonly retained items are sponges, followed by catheter guidewires and other (a broad category encompassing a wide variety of items) [11].

In addition to harming patients and contributing to distrust in the medical system, the unintended retention of foreign objects significantly contributes to patient care costs [13]. The average total cost of care related to unintended retained foreign objects is $166,000 to $200,000 [13].

According to the sentinel event data, the most common root causes of unintended retained foreign objects reported to the Joint Commission are [13]:

- The absence of policies and procedures
- Failure to comply with existing policies and procedures
- Problems with hierarchy and intimidation
- Failure in communication with physicians
- Failure of staff to communicate relevant patient information
- Inadequate or incomplete education of staff

WRONG-SITE SURGERY

Operating on the wrong part of a patient's body is an obvious sign that there is a problem in the operating room system. Interestingly, wrong-site surgery occurred more commonly in orthopedic procedures than in all other surgical specialties combined. The American Academy of Orthopaedic Surgeons takes this issue seriously, and it has taken special steps to eliminate the problem. For example, it recommends that a surgeon sign their initials at the correct site of surgery with an indelible pen. Unless the initials are visible, the surgeon should not make an incision [12]. Writing "NO" in large black letters on the side not to be operated on was suggested in the past, but this is discouraged due to possible confusion with the surgeon's initials. In spinal surgery, the Academy recommends that an intraoperative radiograph and radiopaque marker be used to determine the exact vertebral level of spinal surgery [12]. Whatever the mechanism used to prevent and reduce the incidence of this error, it is clear that this is not just the surgeon's problem. All operating room personnel, including physicians, nurses, technicians, anesthesiologists, and other preoperative allied health personnel, should monitor procedures to ensure verification procedures are followed, especially for high-risk procedures.

Due to the prevalence of wrong-site, wrong-procedure, and wrong-person surgeries, the Joint Commission, along with more than 50 professional healthcare organizations, convened two summits to help reduce the occurrence of these errors. The first summit, convened in 2003, developed a Universal Protocol that consisted of the following: a preprocedure verification process; marking the operative/procedure site with an indelible marker; taking a "time-out" with all team members immediately before starting the procedure; and adaptation of the requirements to all procedure settings, including bedside procedures. However, the incidence of wrong-site surgeries continued to increase, and in 2007 and 2010, additional summits were organized to pinpoint barriers in compliance and discover new strategies to eliminate these errors [14]. As of 2019, the Universal Protocol has been incorporated into the National Patient Safety Goal chapter of the Joint Commission accreditation manual [15].

PATIENT SUICIDE

It is estimated that between 48 and 65 hospital inpatient suicides occur per year in the United States. Most of these cases (31 to 52) occur in psychiatric units or involve psychiatric inpatients. The most common method is hanging [50]. Times of care transition are particularly risky, with a 200% increase in risk in the week after discharge from a psychiatric facility; the elevated risk continues for four years [18]. Other risk factors include previous suicide attempt or self-injury, mental or emotional disorders, history of trauma or loss, serious illness or chronic pain, substance use disorder, social isolation, and access to lethal means.

The most common root cause documented for patient suicide reported between 2010 and 2014 was shortcomings in assessment, most commonly psychiatric assessment [18]. In addition, nearly 25% of behavioral health facilities accredited by the Joint Commission were found noncompliant with the requirement to conduct an adequate suicide risk assessment in 2014.

The Joint Commission has recommended a number of suicide risk reduction strategies, including [18]:

- Review each patient's personal and family medical history for suicide risk factors.
- Screen all patients for suicide ideation, using a brief, standardized, evidence-based screening tool.
- Review screening questionnaires before the patient leaves the appointment or is discharged.
- Establish a collaborative, ongoing, and systematic assessment and treatment process with the patient involving the patient's other providers, family, and friends, as appropriate.
- To improve outcomes for at-risk patients, develop treatment and discharge plans that directly target suicidality.
- Educate all staff in patient care settings about how to identify and respond to patients with suicide ideation.
- Document decisions regarding the care and referral of patients with suicide risk.

A simple review of these measures demonstrates that healthcare providers can avoid the devastating impact of an inpatient suicide by implementing routine preventative strategies, such as removing harmful items and careful screening through the admission and discharge processes.

OPERATIVE AND POSTOPERATIVE COMPLICATIONS

Many of the sentinel events reported to the Joint Commission regarding operative and postoperative complications occurred in relation to nonemergent procedures, such as interventional imaging and/or endoscopy, tube or catheter insertion, open abdominal surgery, head and neck surgery, orthopedic surgery, and thoracic surgery [17]. The majority of the reporting healthcare facilities cited miscommunication as the primary root cause. Other identified causes include failure to follow established procedures, incomplete preoperative assessment, inconsistent postoperative monitoring procedures, and failure to question inappropriate orders. In order to reduce the risk, reporting facilities have identified a number of strategies, including improving staff orientation and training, increasing educational opportunities for physicians, clearly defining expected channels of communication, and monitoring consistency of compliance with procedures. Healthcare facilities should review postoperative patient monitoring procedures to ensure an adequate level appropriate to the needs of the patient, regardless of the setting (e.g., operating room, endoscopy suite, radiology department) [17]. Based upon these findings, it is clear that direct communication among healthcare providers is key to preventing operative and postoperative complications. Healthcare facilities should provide more staff education regarding preventative measures, and healthcare providers can do their part by engaging in a healthy and mutual respect for all of the members of the healthcare team [17].

MEDICATION ERRORS

Unquestionably, medication errors are one of the most common causes of avoidable harm to patients. These errors may occur at any of these critical points: when ordered or prescribed by a physician; during documentation; while transcribing; when dispensed by a pharmacist; when administered by a nurse; or during monitoring.

The National Coordinating Council for Medication Error Reporting and Prevention defines a medication error as [20]:

> Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems, including prescribing: order communication; product labeling; packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

It has been estimated that up to 50% of medication errors are caused by a provider writing the wrong medication, the wrong route or dose, or the wrong frequency, and nearly 75% of medication errors have been attributed to distraction of the care provider [24]. In addition, a number of medication errors can be linked to the prescriber who continually uses potentially dangerous abbreviations and dose expressions. Despite repeated warnings by the Institute for Safe Medication Practices about the dangers associated with using certain abbreviations when prescribing medications, this practice continues. To eliminate this factor, there are fairly simple steps that can eliminate much confusion. Prescribers should [21]:

- Avoid the use of the symbol "U" or "u" but rather spell "units" when ordering drugs, such as insulin.
- Spell out medication names completely rather than using abbreviations and acronyms.
- Avoid using abbreviations for "daily" (QD), "every other day" (QOD), or "four times daily" (QID), which are easily confused.
- Use leading zeros before a decimal point (e.g., 0.2 mg instead of .2 mg), and do not use trailing zeros (e.g., 2 mg instead of 2.0 mg).
- Write out "morphine sulfate" and "magnesium sulfate" instead of using the abbreviations (MS, MSO_4, $MgSO_4$).

The Institute for Safe Medication Practices publishes a list of error-prone abbreviations, symbols, and dose designations online at https://www.ismp.org/recommendations/error-prone-abbreviations-list.

Other factors contributing to prescriber errors are illegible or confusing handwriting and, a frequently cited cause of many adverse and sentinel events, the failure of healthcare providers to assess risk and prevent errors. Addressing illegibility may include developing appropriate policies and procedures, tracking and trending patterns, and evaluating results through peer review committees. Improving communication might include developing protocols for the use of verbal orders to assure that those from an onsite practitioner would be limited to an emergency situation only. No verbal orders should be taken for certain medications, such as for chemotherapy, and all verbal orders should be repeated for clarification and, whenever possible, reiterated to a third person. Another method of improving communication might involve reviewing the hospital formulary in collaboration with the Pharmacy and Therapeutics Committee of the medical staff to limit, where appropriate, the number of therapeutically and generically equivalent products [22].

It has been estimated that between 0.2% and 10% of prescriptions are dispensed incorrectly [23]. The three most common dispensing errors are: dispensing an incorrect medication, dosage strength, or dosage form; miscalculating a dose; and failing to identify drug interactions or contraindications [24]. Safe medication dispensing practices may include a number of risk reduction strategies to reduce the incidence of errors that may cause harm to patients [22; 25; 54; 61]:

- Ensure that appropriate and current drug reference texts and/or online resources are immediately available to pharmacy personnel.
- Ensure that essential patient information, such as allergies, age, weight, current diagnoses, pertinent lab values, and current medication regimen, is available to the pharmacist prior to the dispensing of a new medication order.
- Require clarification of any order that is incomplete, illegible, or otherwise questionable using an established process for resolving questions.
- Whenever possible, dispense dosage units in a ready-to-administer form.
- Dispense single-dose vials and ampoules rather than multidose vials.
- Select oral rather than injectable routes, when possible.
- Require that a pharmacist double-check all mathematical calculations for neonatal and pediatric dilutions, parenteral nutrition solutions, and other compounded pharmaceutical products.
- Create an environment for the dispensing area that minimizes distractions and interruptions, provides appropriate lighting, air conditioning, and air flow, safe noise levels, and includes ergonomic consideration of equipment, fixtures, and technology.
- Require that a second pharmacist double-check the accuracy of order entry and dose calculations for all orders involving antineoplastic agents and other high-risk drugs dispensed by the pharmacy.
- Enhance the awareness of look-alike and sound-alike medications, and use warning signs to help differentiate medications from one another, especially when confusion exists between or among strengths, similar looking labels, or similar sounding names.
- Separate look-alike and sound-alike medications in pharmacy dispensing areas or consider repackaging or using different vendors.
- Follow-up and periodically evaluate the need for continued drug therapy for individual patients.

Once again, communication is likely the key to avoiding dispensing errors. Pharmacists should work closely with their staff to ensure that proper protocols are followed, and most importantly, when questions arise regarding a prescription, the pharmacist should take the time to contact the prescriber directly to obtain clarification.

The healthcare provider who has the responsibility to administer a medication has the final opportunity to avoid a mistake. In most cases, particularly in inpatient settings, this responsibility falls to the nurse. Nurses are often taught in nursing school to review the five "rights" prior to administering any medication: the right patient is given the right drug in the right dose by the right route at the right time [26]. Medication errors generally fall into four categories, which mimic

these five "rights." The first is the failure to follow procedural safeguards, such as ensuring that essential patient information, including allergies, age, weight, and current medication regimen, is available. The second is unfamiliarity with a drug. In one case, a jury determined that a nurse was negligent for giving a drug without having reviewed the literature, which stated that the necessary precautions for the administration of the drug required the specialized skill of an anesthesiologist. The third category of drug administration is failure to use the correct mode of administration. A nurse in Delaware was held liable for administering a medication by injection after an order had been written to change the route to oral. The final category involves failure to obtain clarification if an order is incomplete, illegible, or otherwise questionable. In a case tried in Louisiana, a nurse was held liable for administering a medication that a physician ordered, notwithstanding that the dose was excessive. The nurse's administration of the drug led to the patient's death [27].

In addition, healthcare facilities should implement appropriate guidelines, policies, and procedures to ensure safe medication administration practice. These policies should require that staff members who administer medications [24; 25; 54; 61]:

- Are knowledgeable about the drug's uses, precautions, contraindications, potential adverse reactions, interactions, and proper method of administration
- Resolve questions prior to medication administration
- Only administer medications that have been properly labeled with medication name, dose to be administered, dosage form, route, and expiration date
- Utilize a standard medication administration time schedule and receive education on how and when to incorporate newly started medication orders safely into the standardized schedule
- Have a second person verify a dosage calculation if a mathematical calculation of a dose is necessary
- Receive adequate education on the operation and use of devices and equipment used for medication administration (for example, patient-controlled anesthesia pumps and other types of infusion pumps)
- Have another person double-check infusion pump settings when critical, high-risk drugs are infused
- Document all medications immediately after administration

Finally, healthcare facilities should have proper quality assurance measures in place to monitor medication administration practices. Included among these would be protocols and guidelines for use with critical and problem-prone medications to help optimize therapies and minimize the possibility of adverse events and to integrate "triggers" to indicate the need for additional clinical monitoring [25].

It is important to note that the pediatric population is especially vulnerable to medication errors. When children are prescribed adult medications, care must be taken to adjust dosage according to weight, requiring the physician to use pediatric-specific calculations. Also, many healthcare settings are not trained to care for the pediatric patient. Intolerance due to physiologic immaturity is also a factor in adverse response to medications, and in many cases, this population cannot communicate their discomfort due to adverse reactions. Risk reduction strategies include standardizing and effectively identifying medications and processes for drug administration, ensuring pharmacy oversight, and using technology, such as medication dispensing programs, infusion pumps, and bar-coding, judiciously [28].

COMMON MISDIAGNOSES

As Florida healthcare professionals, it is important to be aware that in addition to wrong-site/wrong-procedure surgery, several medical conditions also continue to be misdiagnosed. As of 2024, the Florida Board of Medicine has determined the five most misdiagnosed conditions to be [29]:

- Oncology-related conditions
- Gastroenterology-related issues
- Cardiology-related issues
- Neurologic conditions
- Infectious disease-related conditions

It is important to be aware of the possibility of misdiagnosis and incorporate this knowledge into practice.

Oncology-Related Conditions

The early detection and diagnosis of cancers is crucial for selecting the appropriate treatment approach and to ensure an optimum outcome. However, an estimated 12% of cancer patients are initially misdiagnosed, and the missed or delayed diagnosis of cancers remains a significant cause of medical malpractice claims [30; 31]. The causes of missed diagnoses vary widely among cancers in different parts of the body. In many cases, patients who do not fit the typical profile for a specific cancer (e.g., young age) may be underdiagnosed, and it is important that cancer is considered as part of the differential diagnosis in ambiguous cases [31; 32; 33]. In order to prevent missed or delayed cancer diagnosis, practitioners may take steps to ensure adherence to clinical guidelines for screening and diagnosis, use tools to facilitate communication, and engage strategies to ensure appropriate follow-up [55].

Gastroenterology-Related Conditions

Gasteroenterologic conditions may present with nonspecific complaints (e.g., abdominal pain, nausea) common to a variety of illnesses, complicating and delaying diagnosis. In one study of patients with pancreatic cancer, more than 30% were initially misdiagnosed, most commonly with gall bladder disease [58]. Diagnosis and screening for gastrointestinal disorders may be complicated by a lack of definitive test (e.g., irritable bowel syndrome) or by limits on screening recommendations (e.g., colorectal cancer). However, delayed diagnosis can lead to worsening conditions and poorer prognosis.

In general, gastrointestinal syndromes/symptoms may be classified into three general diagnostic categories: organic, motility, or functional disorders [59; 60]. Functional GI disorders are idiopathic disorders of gut-brain interaction and, unlike organic and motility disorders, diagnosis involves identification of symptom clusters. As such, misdiagnosis is more common.

Another important consideration is GI symptom-specific anxiety, an important perpetuating factor that describes threatening interpretation and out-of-proportion behavioral response to GI sensations. This anxiety to real GI symptoms and the frequency of psychiatric comorbidity can lead to functional GI syndromes being dismissed as psychological or psychosomatic in nature.

Cardiology-Related Issues

The clinical presentation of chest pain has many possible etiologies, ranging from benign (e.g., panic/anxiety, pneumonia, peptic ulcer, gastroesophageal reflux disease, and pericarditis) to life-threatening (e.g., pulmonary embolism, acute coronary syndrome [ACS], aortic dissection, and pneumothorax). In many cases, it is best to rule out the more urgently threatening possibilities before testing for other causes.

Of the potentially life-threatening causes of chest pain, ACS is the most prevalent. Although a large percentage of individuals with suspected ACS will be seen initially in emergency departments, patients in any healthcare setting, regardless of other diagnoses, may abruptly develop chest pain suspicious for ACS. When a patient presents with clinical signs suspicious for myocardial infarction, immediate medical intervention is directed at confirming a diagnosis and stratifying the person's risk for adverse events such as cardiac arrest and severe/significant damage to the myocardium [41]. It is important to note that while some patients will present with classic ACS-related chest pain (tightness, sensation of pressure, heaviness, crushing, vise-like, aching pain in the substernal or upper left chest), many patients, particularly women and older patients, will present with "atypical" ACS-related chest pain [45; 46]. Words commonly used to describe "atypical" chest pain associated with ACS include numbness, tingling, burning, stabbing, or pricking. Atypical chest pain location includes any area other than substernal or left sided, such as the back, area between shoulder blades, upper abdomen, shoulders, elbows, axillae, and ears [43; 44; 45; 46]. Aside from atypical clinical presentation, other possible causes of missed ACS diagnosis include failure of interpretation of the history, failure to correctly interpret the electrocardiogram, failure to perform an electrocardiogram when necessary, and lack of proper use of cardiac enzyme test [47].

Infectious Disease-Related Conditions

Acute infection was the most commonly misdiagnosed disease in one study, with the potential adverse outcomes of sepsis, organ damage, and even death [37]. The presentation of infectious diseases may be atypical in certain populations (e.g., the elderly), making detection even more difficult. In one survey of physicians, delayed diagnoses were found to commonly occur with tuberculosis, nontuberculous mycobacterial infections, syphilis, epidural abscess, infective endocarditis, and endemic fungal infections (e.g., histoplasmosis, blastomycosis) [38]. Diseases with general symptoms and varied presentations (e.g., Lyme disease) also present complicated clinical pictures. Adherence to established guidelines for the diagnosis and treatment of specific infectious diseases and attentive patient assessment and history are recommended in order to improve diagnostic accuracy [39; 40; 42]. In addition, early consultation with an infectious disease specialist has been identified as potentially mitigating factor [38].

Neurologic Related Conditions

Delayed or missed diagnoses of neurologic conditions may result in serious morbidity and mortality. Headaches are a common presenting condition in acute and primary care, and an estimated 5% of all patients admitted to emergency departments have neurologic symptoms [34]. Acute headache with neurologic symptoms may be misdiagnosed as stroke [35; 64]. In addition, missed spinal fracture diagnoses are one of the leading causes of malpractice claims against radiologists [48].

One of the most common neurologic conditions is headache; however, it has been estimated that 50% of migraine patients remain undiagnosed or misdiagnosed, and only a small number (8% to 10%) of individuals with migraine take migraine-specific medications such as triptans or ergotamines [65; 66]. Patients suffering from daily migraines may be misdiagnosed with chronic sinusitis or rhinitis and repeatedly and unsuccessfully treated with broad-spectrum antibiotics [62; 63]. The diagnosis of migraine is based solely on a constellation of signs and symptoms, and a comprehensive medical and neurological examination is required to exclude secondary headache [56]. Useful evidence-based clinical guidelines for migraine screening have been developed and are summarized in the mnemonic POUND: pulsatile headache; one-day duration (4 to 72 hours); unilateral location; nausea or vomiting; and disabling intensity [57]. Competence of the clinician and effective communication with the patient play a crucial role in the diagnosis of migraine.

OTHER CONSIDERATIONS FOR PATIENT SAFETY

The most important issue to improving patient safety is being aware of the particular safety hazards that may exist for various patient populations and on particular specialty units. In addition, education of the patient and the family should be a priority.

Infants and young children are not developmentally or cognitively able to participate in care and decision making, thus putting them at higher risk, especially for medication errors. In addition, when a medication error occurs in this population, infants and young children are at higher risk because of their physical immaturity and increased sensitivity to the effects of

drugs. The family or guardian of a pediatric patient should be encouraged to ask questions, especially if something seems wrong. In addition, a meta-analysis found that computerized provider order entry with clinical decision support reduced pediatric medication errors by 36% to 87% [51]. As such, the adoption of electronic support systems may help to reduce or eliminate these errors.

An estimated 30% of individuals 65 years of age or older who are living in the community fall each year [52]. Older patients may have poor vision, as a result of cataracts, glaucoma, and/or macular degeneration, and cardiovascular problems, which might result in syncope or postural hypotension. These conditions may affect patients' balance and stability. Bladder dysfunction, such as nocturia, may cause an elderly patient to have to ambulate more during the night in an unfamiliar environment, thereby increasing the risk of a fall. Lower extremity dysfunctions, such as arthritis, muscle weakness, or peripheral neuropathy, may make it more difficult to ambulate at any time. In addition to being at greater risk for falls, the elderly are also more prone to medication errors as their ability to understand instructions or to recognize an unfamiliar medication may be affected by dementia or other cognitive disorders. Interventions that can help prevent falls in the elderly include exercise programs, tai chi, vision improvement (e.g., first cataract surgery), and multifactorial assessment and intervention [52].

There are also unique factors that increase the risk of medical errors on specialty units. For instance, in critical care units, patients may be suffering from environmental psychosis, which could inhibit participation in their care. This is also true of lethargic and comatose patients. These patients are at particular risk because they cannot participate in the identification process. On psychiatric wards, patients may be suicidal or depressed, which may cause them to act out or attempt to harm themselves or others. Patients may also experience orthostatic side effects due to certain psychiatric medications, which may increase the incidence of falls. Obstetric patients are at higher risk for falls because they may have decreased sensation and mobility due to administration of epidural anesthesia, and they may also suffer from excessive blood loss, which could lead to postural hypotension [49]. Again, the key is identifying the unique needs of the particular population.

With regard to education, a number of organizations have developed guidelines to facilitate the role of patients as their own safety advocates. These guidelines are not intended to shift the burden of monitoring medical error to patients. Rather, they encourage patients to share responsibility for their own safety. As healthcare professionals, we should ensure that all of our patients are familiar with these guidelines. The Agency for Healthcare Research and Quality has developed a "Patient Fact Sheet" that outlines 20 tips for patients to help prevent medical errors [53]. Although some of these suggestions may seem extreme, many patients now desire to have a more active role in their care. Some of these items have become routine or are currently required, such as consultations by pharmacists when a patient picks up a prescribed medication.

USE OF AN INTERPRETER

As a result of the evolving racial and immigration demographics in the United States, interaction with patients for whom English is not a native language is inevitable. Because patient education is such a vital aspect of preventing medical errors, it is each practitioner's responsibility to ensure that information and instructions are explained in such a way that allows for patient understanding. 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 are more than passive agents who translate and transmit information back and forth from party to party. They should be professionally trained in ethics, accuracy, completeness, and impartiality. Furthermore, it is the interpreter's role to negotiate cultural differences and promote culturally responsive communication and practice. 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 diagnostic procedures, treatment options, or medication/treatment measures is being provided, the use of an interpreter should be considered.

CONCLUSION

Although the United States has one of the top healthcare systems in the world, it is apparent that the numbers of medical errors are at unacceptably high levels. The consequences of medical errors are often more severe than the consequences of mistakes in other industries. They may lead to death or to serious and long-term disability, which underscores the need for aggressive action in this area. As a starting point, we should become an active part of the solution. This will only happen if all healthcare professionals voice their concerns when they identify problems in a system or process. In addition, we should actively participate in the root cause analysis process, understanding that the goal is not to assign blame, but rather to identify how we can improve the process to provide the best quality care to our patients. Medical errors are costly, not only because patients may lose their lives or livelihoods, but also because patients lose trust in the system and colleagues lose faith in each other. To preserve the integrity of our system, we must correct this problem, and the solution begins with each of us.

Customer Information/Answer Sheet/Evaluation insert located between pages 64–65.

COURSE TEST
#91334 MEDICAL ERROR PREVENTION AND ROOT CAUSE ANALYSIS

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 2 credit activity must be completed by August 31, 2025.

1. **The Institute of Medicine's (IOM) Committee on Quality of Healthcare in America defines error as the failure of a planned action to be completed as intended or the use of a wrong plan to achieve an aim.**
   A) True
   B) False

2. **Patient rape is an example of a sentinel event subject to review by the Joint Commission.**
   A) True
   B) False

3. **A "thorough" root cause analysis is one in which the participants identify risk points and their potential contributions to this type of event.**
   A) True
   B) False

4. **A credible root cause analysis must be based upon a survey of everyone employed at the healthcare institution.**
   A) True
   B) False

5. **A wrong-site surgical procedure that did not result in the death of the patient must be reported to the risk manager within three business days according to Florida law.**
   A) True
   B) False

6. **The Joint Commission prepares and distributes Sentinel Event Alerts in order to recommend ways in which the healthcare facility can terminate employees whose actions result in a sentinel event.**
   A) True
   B) False

7. **Infant abduction is among the most common sentinel events reported to the Joint Commission.**
   A) True
   B) False

8. **The most common root cause documented for patient suicide was shortcomings in assessment, most commonly psychiatric assessment.**
   A) True
   B) False

9. **A medication error may occur when ordered by a physician, administered by a nurse, or dispensed by a pharmacist.**
   A) True
   B) False

10. **Approximately 32% of patients with cancer are initially misdiagnosed.**
    A) True
    B) False

Be sure to transfer your answers to the Answer Sheet insert located between pages 64–65.
PLEASE NOTE: Your postmark or facsimile date will be used as your test completion date.

Domestic Violence: The Florida Requirement

This course fulfills the Florida requirement for 2 hours of Domestic Violence education.

Audience

This course is designed for all Florida healthcare professionals required to complete domestic violence education.

Course Objective

The purpose of this course is to enable healthcare professionals in all practice settings to define domestic violence and identify those who are affected by domestic violence in the United States. This course describes how a victim can be accurately diagnosed and identifies the community resources available in the state of Florida for domestic violence victims.

Learning Objectives

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

1. Define domestic violence and its impact on health care.
2. Cite the general prevalence of domestic violence on a national and state level and identify state laws pertaining to the issue.
3. Describe how to screen and assess individuals who may be victims or perpetrators of domestic violence, including the importance of conducting a culturally sensitive assessment.
4. Identify community resources presently available for domestic violence victims and their perpetrators throughout Florida concerning legal aid, shelter, victim and batterer counseling, and child protection services.

Faculty

Marjorie Conner Allen, BSN, JD, received her Bachelor of Science in Nursing degree from the University of Florida, Gainesville, in 1984. She began her nursing career at Shands Teaching Hospital and Clinics at the University of Florida, Gainesville. While practicing nursing at Shands, she gave continuing education seminars regarding the nursing implications for dealing with adolescents with terminal illness. In 1988, Ms. Allen moved to Atlanta, Georgia where she worked at Egleston Children's Hospital at Emory University in the bone marrow transplant unit. (A complete biography can be found at NetCE.com.)

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

Faculty Disclosure

Contributing faculty, Marjorie Conner Allen, BSN, JD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Contributing faculty, Alice Yick Flanagan, PhD, MSW, 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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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.

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

INTRODUCTION

Domestic violence continues to be a prevalent problem in the United States today. Because of the number of individuals affected, it is likely that most healthcare professionals will encounter patients in their practice who are victims. Accordingly, it is essential that healthcare professionals are taught to recognize and accurately interpret behaviors associated with domestic violence. It is incumbent upon the healthcare professional to establish and implement protocols for early identification of domestic violence victims and their abusers. In order to prevent domestic violence and promote the well-being of their patients, healthcare professionals in all settings should take the initiative to properly assess all women for abuse during each visit and, for those women who are or may be victims, to offer education, counseling, and referral information.

Victims of domestic violence suffer emotional, psychologic, and physical abuse, all of which can result in both acute and chronic signs and symptoms of physical and mental disease, illness, and injury. Frequently, the injuries sustained require abused victims to seek care from healthcare professionals immediately after their victimization. Subsequently, physicians and nurses are often the first healthcare providers that victims encounter and are in a critical position to identify domestic violence victims in a variety of clinical practice settings where victims receive care. Accordingly, each healthcare professional should educate himself or herself to enhance awareness of the presence of abuse victims in his or her particular practice or clinical setting.

Specifically, healthcare professionals should be aware of the signs and symptoms associated with domestic violence. In addition, when family violence cases are identified, there should be a plan of action that includes providing information on, and referral to, local community resources related to legal aid, sheltering, victim counseling, batterer counseling, advocacy groups, and child protection.

DEFINING DOMESTIC VIOLENCE

Domestic violence, which is sometimes also referred to as spousal abuse, battering, or intimate partner violence (IPV), refers to the victimization of an individual with whom the abuser has or has had an intimate or romantic relationship. Researchers in the field of domestic violence have not agreed on a uniform definition of what constitutes violence or an abusive relationship. The Centers for Disease Control and Prevention (CDC) defines IPV as, "violence or aggression that occurs in a romantic relationship" [1]. According to the Florida Department of Children and Families, domestic violence is "a pattern of abusive behaviors that adults use to maintain power and control over their intimate partners or former partners. People who abuse their partners use a variety of tactics to coerce, intimidate, threaten, and frighten their victims" [2]. Domestic violence may include physical violence, sexual violence, emotional abuse, economic abuse, isolation, pet abuse, threats relating to children, and a variety of other behaviors meant to increase fear, intimidation, and power over the victim [2]. Florida law defines domestic violence as "any assault, aggravated assault, battery, aggravated battery, sexual assault, sexual battery, stalking, aggravated stalking, kidnapping, false imprisonment, or any criminal offense resulting in physical injury or death of one family or household member by another family or household member" [3]. Family or household members, according to Florida definition, must "be currently residing or have in the past resided together in the same single dwelling unit" [3]. Domestic violence knows no boundaries. It occurs in intimate relationships regardless of race, religion, culture, or socioeconomic status [2].

Whatever the definition, it is important for healthcare professionals to understand that domestic violence, in the form of emotional and psychologic abuse, sexual abuse, and physical violence, is prevalent in our society. Because of the similar nature of the definitions, this course will use the terms "domestic violence" and "IPV" interchangeably.

NATIONAL AND STATE STATISTICS AND LEGISLATION

Domestic violence is one of the most serious public health problems in the United States [4]. More than 36.4% of women and 33.6% of men have a lifetime history of IPV [4]. In Florida, the weighted lifetime prevalence of IPV (including rape, physical violence, and/or stalking) is 37.4% among women and 29.3% among men [5]. Although many of these incidents are relatively minor and consist of pushing, grabbing, shoving, slapping, and hitting, IPV resulted in approximately 1,500 deaths in the United States in 2019, with 214 of those deaths occurring in Florida in the same year. Statistics indicate a slightly higher rate in 2020, with 217 deaths in Florida in 2020 [7; 8]. One of the difficulties in addressing the problem is that abuse is prevalent in all demographics, regardless of age, ethnicity, race, religious denomination, education, or socioeconomic status [2].

Victims of abuse often suffer severe physical injuries and will likely seek care at a hospital or clinic. The health and economic consequences of domestic violence are significant. Statistics vary from report to report, and due to the lack of studies on the national cost of domestic violence, the U.S. Congress funded the CDC to conduct a study to determine the cost of domestic violence on the healthcare system [9]. The 2003 CDC report, which relied on data from the National Violence Against Women Survey conducted in 1995, estimated the costs of IPV by measuring how many female victims were nonfatally injured; how many women used medical and mental healthcare services; and how many women lost time from paid work and

household chores. The estimated total annual cost of IPV against women in the 1995 survey was more than $5.8 billion [9]. When updated to 2017 dollars, the amount was more than $9.3 billion annually. The costs associated with IPV at this time would be considerably more, but no further studies have been conducted [10]. It should be noted that the costs of any one victimization may continue for years; therefore, these statistics most likely underestimate the actual cost of IPV [9].

The national rate of nonfatal domestic violence against women declined 72% between 1993 and 2011 [11]. The rate of overall violent crime fell by nearly 60% in this same time period [11]. Studies reveal that several factors may have contributed to the reduction in violence, including a decline in the marriage rate and decrease of domesticity, better access to federally funded domestic violence shelters, improvements in women's economic status, and demographic trends, such as the aging of the population [13; 14]. Of note, declines in the economy and stress associated with financial hardship and unemployment are significant contributors to IPV in the United States. Following the economic downturn in late 2008, there was a significant increase in the use of the National Domestic Violence Hotline in 2009, with more than half of victims reporting a change in household financial situation in the last year [15]. This trend continued with the COVID-19 pandemic, with stressors from lockdown orders, unemployment, financial insecurity, childcare and homeschool responsibilities, and poor coping strategies (e.g., substance abuse) increasing the rate of domestic violence. Reports showed a 9.7% increase in domestic violence calls for service in the first two months state-mandated lockdowns were imposed; furthermore, the National Commission on COVID-19 and Criminal Justice reported an increase of 8.1% in domestic violence incidents within the first months of mandated stay-at-home orders [6].

FLORIDA

In response to troubling domestic violence statistics, Governor Lawton Chiles appointed a Task Force on Domestic Violence on September 28, 1993, to investigate the problems associated with domestic violence in Florida and to compile recommendations as to how the problems should be approached and ultimately resolved. On January 31, 1994, the Task Force issued its first report on domestic violence. This report recommended standards to accurately measure the extent of domestic violence and strategies for increasing public awareness and education. It identified programs and resources that are available to victims in Florida, made legislative and budgetary suggestions for needed changes, provided a methodology for implementing these changes, and identified areas of domestic violence that require further study.

As a result of this report, Florida enacted legislation during the 1995 session implementing various suggestions of the Task Force. Specifically, the Legislature amended Section 455.222 of the Florida Statutes to require that all physicians, osteopaths, nurses, dentists, dental hygienists, midwives, psychologists, and psychotherapists obtain, as part of their biennial continuing education requirements, a one-hour continuing education course on domestic violence [17]. In June of 2006, Governor Jeb Bush signed into law House Bill 699. The bill, which went into effect July 1, 2006, changed the domestic violence continuing education requirement from one hour every renewal period to two hours every third renewal period.

In 1997, at the request of the Governor's Task Force, a workgroup was established by the Florida Department of Law Enforcement (FDLE) to evaluate the feasibility of tracking incidents of domestic violence in the state [18]. This resulted in the creation of the Domestic Violence Data Resource Center (DVDRC). The original mission of the DVDRC was to collect information related to domestic violence and to report and maintain the information in a statewide tracking system [19]. Domestic Violence Fatality Review Teams were established to examine those cases of domestic violence that resulted in a fatality and identify potential changes in policy or procedure that might prevent future deaths. The teams were comprised of representatives from law enforcement, the courts, social services, state attorneys, domestic violence centers, and others who may come into contact with domestic violence victims and perpetrators [20]. In 2000, the creation of Florida Statute 741.316 required the FDLE to annually publish a report based on the data gathered by the Fatality Review Teams [19]. Due to budgetary constraints, responsibility of compiling this data transferred to the Department of Children and Families in 2008 [21].

As part of Governor Jeb Bush's initiative, the "Family Protection Act" was signed into law in 2001. The act requires a 5-day mandatory jail term for any crime of domestic battery in which the perpetrator deliberately injures the victim. The law also makes a second battery crime a felony offense, treating offenders as serious criminals. Additional legislation, signed into law in 2002, includes Senate Bills 716 and 1974. Senate Bill 716 protects domestic violence victims by including dating relationships of six months in the definition of domestic violence laws. Senate Bill 1974 requires judges to inform victims of their rights, including the right to appear, be notified, seek restitution, and make a victim-impact statement. Governor Bush also created the Violence Free Florida campaign to increase public awareness of domestic violence issues [22].

In 2003, Governor Bush signed House Bill 1099, which transferred funding authority of the Florida Domestic Violence Trust Fund from the Department of Children and Families to the Florida Coalition Against Domestic Violence. According to the Domestic Violence in Florida 2010–2011 Annual Report to the Legislature, this has strengthened domestic violence services provided by streamlining the process of allocating funds [23].

In 2007, the Domestic Violence Leave Act was signed into law by Governor Charlie Crist [21]. This law requires employers with 50 or more employees to provide guaranteed leave for domestic violence issues.

In 2020, the FDLE reported 106,736 domestic violence offenses [8]. In general, domestic violence rates have been declining since 1998. An estimated 19.5% of domestic violence incidents involved spouses and 27.8% involved cohabitants; 11.6% of the victims were parents of the offenders. Domestic violence offenses resulted in the death of 217 victims in Florida in 2020, a number that has been decreasing since 2014 [8]. Domestic violence accounted for 16.9% of the state's murders in 2020 [8].

In their 2019 Annual Report, Fatality Review Teams summarized 31 cases of domestic violence fatalities and near fatalities [49]. The most significant findings included the following observations [49]:

- The perpetrators were predominantly male (94%) with female victims (90%) and had prior criminal histories, non-domestic-violence-related (67%) and for domestic violence specifically (69%).
- In 31% of fatalities, the perpetrators had a known "do not contact" order filed against them, and 13% of perpetrators had a known permanent injunction for protection against them filed by someone other than the victim.
- Substance abuse histories by the perpetrator was identified in 77% of the cases and diagnosed mental health disorders in 45%.
- In most cases, neither the decedent nor perpetrator sought help from the various intervention programs available to them.

To obtain a copy of the most current Florida Statewide Domestic Violence Fatality Review report, please visit https://www.myflfamilies.com/service-programs/domestic-violence/publications.shtml.

IDENTIFYING GROUPS AT RISK FOR DOMESTIC VIOLENCE

Healthcare professionals are in a critical position to identify domestic violence victims in a variety of clinical practice settings. Nurses are often the first healthcare provider a victim of domestic violence will encounter in a healthcare setting and should therefore be prepared to provide care and support for these victims. Although women are most often the victims, domestic violence extends to others in the household as well. For example, domestic violence includes abused men, children abused by their parents or parents abused by their children, elder abuse, and abuse among siblings [3].

Many victims of abuse sustain injuries that lead them to present to hospital emergency departments. Research has found that 49.6% of women seen in emergency departments reported a history of abuse and 44% of women who were ultimately killed by their abuser had sought help in an emergency department in the two years prior to their death [25; 50]. Another study of 993 police-identified female victims of IPV found that only 28% of the women were identified in the emergency department as being victims of IPV [26]. These alarming statistics demonstrate that healthcare professionals who work in acute care, such as hospital emergency rooms, should maintain a high index of suspicion for battering of the patients that they see. Healthcare professionals who work in these settings should work with hospital administrators to establish and institute assessment mechanisms to accurately detect these victims.

For every victim of abuse, there is also a perpetrator. Like their victims, perpetrators of domestic violence come from all socioeconomic backgrounds, races, religions, and walks of life [1; 4]. Accordingly, healthcare professionals should likewise be aware that seemingly supportive family members may, in fact, be abusers.

PREGNANT WOMEN

Because a gynecologist or obstetrician is frequently a woman's primary care physician, the American College of Obstetricians and Gynecologists (ACOG) recommends that all women be routinely assessed for signs of IPV (i.e., physical and psychologic abuse, reproductive coercion, and progressive isolation), including during prenatal visits, and providers should offer support and referral information for those being abused [25]. According to the ACOG, IPV affects as many as 324,000 pregnant women each year [25]. A meta-analysis of 92 independent studies found that the average reported prevalence of emotional abuse during pregnancy was 28.4%, physical abuse was 13.8%, and sexual abuse was 8% [51]. As with all domestic violence statistics, these estimates are presumed to be lower than the actual incidence as a result of under-reporting and lack of data on women whose pregnancies ended in fetal or maternal death. This makes IPV more prevalent among pregnant women than some of the health conditions included in prenatal screenings, including pre-eclampsia and gestational diabetes [25]. Because 96% of pregnant women receive prenatal care, this is an optimal time to assess for domestic violence and develop trusting relationships with the women. Possible factors that may predispose pregnant women to IPV include being unmarried, lower socioeconomic status, young maternal age, unintended pregnancy, delayed prenatal care, lack of social support, and use of tobacco, alcohol, or illegal drugs [25; 51].

The overarching problem of violence against pregnant women cannot be ignored, especially as both mother and fetus are at risk. At this particularly vulnerable time in a woman's life, an organized clinical construct leading to immediate diagnosis and medical intervention will ensure that therapeutic opportunities are available to the pregnant woman and will reduce

the potential negative outcomes [29]. Healthcare professionals should also be aware of the possible psychologic consequences of abuse during pregnancy. There is a higher risk of stress, depression, and addiction to alcohol and drugs in abused women. These conditions may result in damage to the fetus from tobacco, drugs, and alcohol and a loss of interest on the part of the mother in her or her baby's health [16; 30]. Possible direct injuries to the fetus may result from maternal trauma [25].

Control of reproductive or sexual health is also a recognized trend in IPV. This type of abuse includes trying to impregnate or become pregnant against a partner's wishes, refusal to use birth control (e.g., condoms, oral contraceptives), or stopping a partner from using birth control [4].

CHILDREN

Children exposed to family violence are at high risk for abuse and for emotional damage that may affect them as they grow older. The Department of Justice estimates that of the 76 million children in the United States, 46 million will be exposed to some type of violence during their childhood [52]. Results of the National Survey of Children's Exposure to Violence indicated that 11% of children were exposed to IPV at home within the last year, and as many as 26% of children were exposed to at least one form of family violence during their lifetimes [31]. Of those children exposed to IPV, 90% were direct eyewitnesses of the violence; the remaining children were exposed by either hearing the violence or seeing or being told about injuries [31]. Of note, according to Florida criminal law, witnessing domestic violence is defined as "violence in the presence of a child if an offender is convicted of a primary offense of domestic violence, and that offense was committed in the presence of a child under age 16 who is a family or household member with the victim or perpetrator" [32].

A number of studies indicate that child witnesses are at increased risk for post-traumatic stress disorder, impaired development, aggressive behavior, anxiety, difficulties with peers, substance abuse, and academic problems than the average child [33; 54; 55]. Children exposed to violence may also be more prone to dating violence (as a perpetrator or a victim), and the ability to effectively cope with partnerships and parenting later in life may be affected, continuing the cycle of violence into the next generation [34; 56].

In addition to witnessing violence, various studies have shown that these children may also become direct victims of violence, and children who both witness and experience violence are at the greatest risk for adverse psychosocial outcomes [53]. Research indicates that between 30% and 65% of husbands who batter their wives also batter their children [27; 35]. Moreover, victims of abuse will often turn on their children; statistics demonstrate that 85% of domestic violence victims abuse or neglect their children. The 2020 Crime in Florida report found that more than 13% of domestic homicide victims were children killed by a parent [8]. Teenage children are also victimized. According to the U.S. Department of Justice, between 1980 and 2008, 17.5% of all homicides against female adolescents 12 to 17 years of age were committed by an intimate partner [36]. Among young women (18 to 24 years of age), the rate is estimated to be 43% in the United States and 8% to 57% globally. Abused teens often do not report the abuse. Individuals 12 to 19 years of age report only 35.7% of crimes against them, compared with 54% in older age groups [28; 37]. Accordingly, healthcare professionals who see young children and adolescents in their practice (e.g., pediatricians, family physicians, school nurses, pediatric nurse practitioners, community health nurses) should have the tools necessary to detect these "silent victims" of domestic violence and to intervene quickly to protect young children and adolescents from further abuse. Without such critical intervention, the cycle of violence will never end.

ELDERLY

Abused and neglected elders, who may be mistreated by their spouses, partners, children, or other relatives, are among the most isolated of all victims of family violence. In a national study conducted by the National Institute of Justice in 2010, 4.6% of participants (community dwelling adults 60 years of age or older) were victims of emotional abuse in the past year, 1.6% physical abuse, 0.6% sexual abuse, 5.1% potential neglect, and 5.2% current financial abuse by a family member [38]. A 2017 study found a self-reported incidence of 11.6% psychological abuse, 2.6% physical abuse, 6.8% financial abuse, 4.2% neglect, and 0.9% sexual abuse [59]. The estimated annual incidence of all elder abuse types is 2% to 10%, but it is believed to be severely under-measured. According to one study, only 1 in 24 cases of elder abuse are reported to the authorities [39].

The prevalence rate of elder abuse in institutional settings is not clear. However, in a 2019 review of nine studies, 64% of elder care facility staff disclosed to having perpetrated abuse against an elderly resident in the past year [40]. In a random sample survey, 24.3% of respondents reported at least one incident of elder physical abuse perpetrated by a nursing home staff member [57].

As healthcare professionals in Florida, which leads the nation in percentage of older residents, it is important to understand that the needs of older Floridians will increase as will the numbers of elder victims of domestic violence. Because elder abuse can occur in family homes, nursing homes, board and care facilities, and even medical facilities, healthcare professionals should remain keenly aware of the potential for abuse. When

abuse occurs between elder partners, it is primarily manifested in one of two ways: either as a long-standing pattern of marital violence or as abuse originating in old age. In the latter case, abuse may be precipitated by issues related to advanced age, including the stress that accompanies disability and changing family relationships [39].

It is important to understand that the domestic violence dynamic involves not only a victim but a perpetrator as well. For example, an adult son or daughter who lives in the parents' home and depends on the parents for financial support may be in a position to inflict abuse. This abuse may not always manifest itself as violence but can lead to an environment in which the elder parent is controlled and isolated. The elder may be hesitant to seek help because the abuser's absence from the home may leave the elder without a caregiver [39]. Because these elderly victims are often isolated, dependent, infirm, or mentally impaired, it is easy for the abuse to remain undetected. Healthcare professionals in all settings should remain aware of the potential for abuse and keep a watchful eye on this particularly vulnerable group.

The U.S. Preventive Services Task Force concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for abuse and neglect in all older or vulnerable adults.

(https://jamanetwork.com/journals/jama/fullarticle/2708121. Last accessed July 26, 2022.)

Strength of Recommendation: I (Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.)

MEN

Statistics confirm that domestic violence is predominantly perpetrated by men against women; however, there is evidence that women also exhibit violent behavior against their male partners [4]. Studies demonstrate approximately 5% of homicides against men are perpetrated by intimate partners [36]. It is persuasively argued that the impact on the health of female victims of domestic violence is generally much more severe than the impact on the health of male victims [42]. Approximately 512,770 women were raped and/or physically assaulted by an intimate partner in 2008, compared to 101,050 men [58]. In addition, 1 in 4 women has been physically assaulted, raped, and/or stalked by an intimate partner, compared with 1 out of every 10 men [1]. Rape, non-contact unwanted sexual experiences, and stalking against men are primarily perpetrated by other men, while other forms of violence against men were perpetrated mostly by women [5]. Male victims of IPV experienced 3 victimizations per 1,000 boys and men 12 years of age or older in 1994, and this rate decreased by 64%, to 1.1 per 1,000, in 2010 [11]. Of all homicides committed against men between 1980 and 2008, 7.1% were committed by an intimate partner [36]. Although women are more often victims of IPV, healthcare professionals should always keep in mind that men can also be victimized and assess accordingly.

LESBIAN, GAY, BISEXUAL, TRANSGENDER, AND QUEER/QUESTIONIONG VICTIMS

Domestic violence exists in lesbian, gay, bisexual, transgender, and queer/questioning (LGBTQ+) communities, and the rates are thought to mirror those of heterosexual women—approximately 25% [43]. However, women living with female intimate partners experience less IPV than women living with men [8]. Conversely, men living with male intimate partners experience more IPV than do men who live with female intimate partners [8]. In addition, 78% of IPV homicide victims reported in 2017 were transgender women or cisgender men [24]. This supports other statistics indicating that IPV is perpetrated primarily by men. A form of abuse specific to the gay community is for an abuser to threaten or to proceed with "outing" a partner to others [41; 43].

Transgender individuals appear to be at particular risk for violence. According to a large national report, transgender victims of IPV were 1.9 times more likely to experience physical violence and 3.9 times more likely to experience discrimination than other members of the LGBTQ+ community [24].

In 2017, an annual national report recorded 52 incidences of hate violence-related homicides of LGBTQ+ people, the highest incident number recorded in its 20-year history [24]. This increasing prevalence of anti-LGBTQ+ violence can exacerbate IPV in LGBTQ+ communities. For example, a person who loses their job because of anti-trans bias may be more financially reliant on an unhealthy relationship. An abusive partner may also use the violence that an LGBTQ+ person experiences from their family as a way of isolating that person further [24].

Because of the stigma of being LGBTQ+, victims may be reticent to report abuse and afraid that their sexual orientation or biologic sex will be revealed. In one study, the three major barriers to seeking help were a limited understanding of the problem of LGBTQ+ IPV, stigma, and systemic inequities [41]. Many in this community feel that support services (e.g., shelters, support groups, crisis hotlines) are not available to them due to homophobia of the service providers. Unfortunately, this results in the victim feeling isolated and unsupported. Healthcare professionals should strive to be sensitive and supportive when working with homosexual patients.

CHARACTERISTICS OF PERPETRATORS OF DOMESTIC VIOLENCE

Abuser characteristics have been studied far less frequently than victim characteristics. Some studies suggest a correlation between the occurrence of abuse and the consumption of alcohol. A man who abuses alcohol is also likely to abuse his mate, although the abuser may not necessarily be inebriated at the time the abuse is inflicted [44]. Domestic violence assessment questionnaires should include questions that explore social drinking habits of both victims and their mates.

Other studies demonstrate that abusive mates are generally possessive and jealous. Another characteristic related to the abuser's dependency and jealousy is extreme suspiciousness. This characteristic may be so extreme as to border on paranoia [12]. Domestic violence victims frequently report that abusers are extremely controlling of the everyday activities of the family. This domination is generally all encompassing and often includes maintaining complete control of finances and activities of the victim (e.g., work, school, social interactions) [12].

In addition, abusers often suffer from low self-esteem and their sense of self and identity is directly connected to their partner [12]. Extreme dependence is common in both abusers and those being abused. Due to low self-esteem and self-worth, emotional dependence often occurs in both partners, but even more so in the abuser. Emotional dependence in the victim stems from both physical and psychologic abuse, which results in a negative self-image and lack of self-worth. Financial dependence is also very common, as the abuser often withholds or controls financial resources to maintain power over the victim [1; 4].

SCREENING FOR DOMESTIC VIOLENCE AND ABUSE

There is no universal guideline for identifying and responding to domestic violence, but it is universally accepted that a plan for screening, assessing, and referring patients of suspected abuse should be in place at every healthcare facility. Guidelines should review appropriate interview techniques for a given setting and should also include the utilization of assessment tools. Furthermore, protocols within each facility or healthcare setting should include referral, documentation, and follow-up. This section relies heavily on the guidelines outlined in the Family Violence Prevention Fund's *National Consensus Guidelines on Identifying and Responding to Domestic Violence Victimization in Health Care Settings*; however, protocols should be customized based on individual practice settings and resources available [35]. The CDC has provided a compilation of assessment tools for healthcare workers to assist in recognizing and accurately interpreting behaviors associated with domestic violence and abuse, which may be accessed at https://www.cdc.gov/violenceprevention/pdf/ipv/ipvandsvscreening.pdf [45].

The U.S. Preventive Services Task Force recommends that that clinicians screen for intimate partner violence (IPV) in women of reproductive age and provide or refer women who screen positive to ongoing support services.

(https://jamanetwork.com/journals/jama/fullarticle/2708121. Last accessed July 26, 2022.)

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

Several barriers to screening for domestic violence have been noted, including a lack of knowledge and training, time constraints, lack of privacy for asking appropriate questions, and the sensitive nature of the subject [35]. Although awareness and assessment for IPV has increased among healthcare providers, many are still hesitant to inquire about abuse [46]. At a minimum, those exhibiting signs of domestic violence should be screened. Although victims of IPV may not display typical signs and symptoms when they present to healthcare providers, there are certain cues that may be attributed to abuse. The obvious cues are physical. Injuries range from bruises, cuts, black eyes, concussions, broken bones, and miscarriages to permanent injuries such as damage to joints, partial loss of hearing or vision, and scars from burns, bites, or knife wounds. Typical injury patterns include contusions or minor lacerations to the head, face, neck, breast, or abdomen and musculoskeletal injuries. These are often distinguishable from accidental injuries, which are more likely to involve the extremities of the body. Abuse victims are also more likely to have multiple injuries than accident victims. When this pattern of injuries is seen, particularly in combination with evidence of old injury, physical abuse should be suspected [44].

In addition to physical signs and symptoms, domestic violence victims also exhibit psychologic cues that resemble an agitated depression. As a result of prolonged stress, various psychosomatic symptoms that generally lack an organic basis often manifest. For example, complaints of backaches, headaches, and digestive problems are common. Often, there are reports of fatigue, restlessness, insomnia, or loss of appetite. Great amounts of anxiety, guilt, and depression or dysphoria are also typical. Women who experienced IPV are also more likely to report asthma, irritable bowel syndrome, and diabetes [4]. Healthcare professionals should look beyond the typical symptoms of a domestic violence victim and work within their respective practice settings to develop appropriate assessment mechanisms to detect victims who exhibit less obvious symptoms.

ASSESSMENT OF IMMEDIATE SAFETY FOR DOMESTIC VIOLENCE VICTIMS
Are you in immediate danger?
Is your partner at the health facility now?
Do you want to (or have to) go home with your partner?
Do you have somewhere safe to go?
Have there been threats or direct abuse of the child(ren) (if applicable)?
Are you afraid your life may be in danger?
Has the violence gotten worse or is it getting scarier? Is it happening more often?
Has your partner used weapons, alcohol, or drugs?
Has your partner ever held you or your child(ren) against your will?
Does your partner ever watch you closely, follow you or stalk you?
Has your partner ever threatened to kill you, him/herself or your child(ren)?
Source: [35] *Table 1*

The unique relationship dynamics of the abuser and abused are not easily detected under the best of circumstances. They may be especially difficult to uncover in circumstances in which the parties are suspicious and frightened, as might be expected when a victim presents to the emergency department. The key to detection, however, is to establish a proper assessment tool that can be utilized in the particular setting and to maintain a keen awareness for the cues described in this course. Screening for IPV should be carried out at the entry points of contact between victims and medical care (e.g., primary care, emergency services, obstetric and gynecologic services, psychiatric services, and pediatric care) [35].

The key to an initial assessment is to obtain an adequate history. Establishing that a patient's injuries are secondary to abuse is the first task. Clearly, there will be times when a victim is injured so severely that treatment of these injuries becomes the first priority. After such treatment is rendered, however, it is important that healthcare professionals not ignore the reasons that brought the victim to the emergency department [35].

ASSESSING DOMESTIC VIOLENCE AND ABUSE

Healthcare providers have reported that even if routine screening and inquiry results in a positive identification of IPV, the next steps of assessing and referring are often difficult, and many feel that they are not adequately prepared [46]. According to the Family Violence Prevention Fund, the goals of the assessment are to create a supportive environment, gather information about health problems associated with the abuse, and assess the immediate and long-term health and safety needs for the patient to develop an intervention [35].

Assessment of domestic violence victims should occur immediately after disclosure of abuse and at any follow-up appointments. Assessing immediate safety is priority. Having a list of questions readily available and well-practiced can help alleviate the uncertainty of how to begin the assessment (***Table 1***). If the patient is in immediate danger, referral to an advocate, support system, hotline, or shelter is indicated [35].

If the patient is not in immediate danger, the assessment may continue with a focus on the impact of IPV on the patient's mental and physical health and the pattern of history and current abuse [35]. These responses will help formulate an appropriate intervention.

CULTURALLY SENSITIVE ASSESSMENT

During the assessment process, a practitioner should be open and sensitive to the patient's worldview, cultural belief systems and how he/she views the illness [47]. This may reduce the tendency to over-pathologize or minimize health concerns of ethnic minority patients.

Pachter proposed a dynamic model that involves several tiers and transactions [48]. The first component of Pachter's model calls for the practitioner to take responsibility for cultural awareness and knowledge. The professional should be willing to acknowledge that he/she does not possess enough or adequate knowledge in health beliefs and practices among the different ethnic and cultural groups he/she comes in contact with. Reading and becoming familiar with medical anthropology is a good first step.

The second component emphasizes the need for specifically tailored assessment [48]. Pachter advocates the notion that there is tremendous diversity within groups. For example, one cannot automatically assume that a Cuban immigrant adheres to traditional beliefs. Often, there are many variables, such as level of acculturation, age at immigration, educational level, and socioeconomic status, that influence health ideologies. Finally, the third component involves a negotiation process between the patient and the professional [48]. The negotiation consists of a dialogue that involves a genuine respect of beliefs. It is important to remember that these beliefs may affect symptoms or appropriate interventions in the case of domestic violence.

Culturally sensitive assessment involves a dynamic framework whereby the practitioner engages in a continual process of questioning. By incorporating cultural sensitivity into the assessment of individuals with a history of being victims or perpetrators of domestic violence, it may be possible to intervene and offer treatment more effectively.

INTERVENTIONS FOR DOMESTIC VIOLENCE AND ABUSE

After the assessment is complete, the patient may or may not want immediate assistance or referral. It is important for healthcare providers to assure patients in a nonjudgmental manner that the decision of what they would like in terms of assistance is their choice and that the provider will help regardless of the decisions they are currently ready to make [35].

If the patient would like to immediately implement a plan of action, information for referral to a local domestic violence shelter to assist the victim and the victim's family should be readily available. The acute situation should be referred immediately to local law enforcement officials. Other resources in an acute situation include crisis hotlines and rape relief centers. After a victim is introduced into the system, counseling and follow-up are generally available by individual counselors who specialize in the care of battered women and their spouses and children. These may include social workers, psychologists, psychiatrists, other mental health workers, and community mental health services. The goals are to make the resources accessible and safe and to enhance support for those who are unsure of their options [35].

In Florida, a 24-hour domestic violence hotline is available for toll-free counseling and information. The number is 800-500-1119. The counselors answering the toll-free line may refer the victim to her or his local domestic violence center. A list of Florida certified domestic violence centers organized by county may also be found on the Florida Department of Children and Families website at https://www.myflfamilies.com/service-programs/domestic-violence. Florida's domestic violence centers provide information and referral services, counseling and case management services, a 24-hour hotline, temporary emergency shelter for more than 24 hours, educational services for community awareness relative to domestic violence, assessment and appropriate referral of resident children, and training for law enforcement personnel.

DOCUMENTATION AND FOLLOW-UP

It is imperative that healthcare professionals document all findings and recommendations regarding domestic violence in the victim's medical record, including a patient's denial of abuse, if applicable. If domestic violence is disclosed, documentation should include relevant history, results of the physical examination, findings of laboratory and other diagnostic procedures, and results of the assessment, intervention, and referral. The medical record can be an invaluable document in establishing the credibility of the victim's story when seeking legal aid [35].

Healthcare professionals should offer a follow-up appointment if disclosure of past or current abuse is present. Reassurance that assistance is available to the patient at any time is critical in helping to break the cycle of abuse [35].

Customer Information/Answer Sheet/Evaluation insert located between pages 64–65.

COURSE TEST
#97923 DOMESTIC VIOLENCE: THE FLORIDA REQUIREMENT

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 2 credit activity must be completed by July 31, 2025.

1. **Most healthcare professionals will encounter patients in their practice who are victims of domestic violence.**
   A) True
   B) False

2. **The Florida Department of Children and Families' definition of domestic violence may include pet abuse, physical abuse, and/or emotional abuse.**
   A) True
   B) False

3. **Florida law defines domestic violence exclusively as spouse abuse or battering.**
   A) True
   B) False

4. **House Bill 1099 strengthened domestic violence services by streamlining the process of allocating funds.**
   A) True
   B) False

5. **Domestic violence resulted in 217 deaths in Florida in 2020.**
   A) True
   B) False

6. **The majority of children exposed to intimate partner violence are direct eyewitnesses.**
   A) True
   B) False

7. **Domestic violence injury patterns are more likely than accidental injuries to involve the extremities of the body.**
   A) True
   B) False

8. **In addition to physical signs and symptoms, domestic violence victims may also exhibit psychologic cues that resemble an agitated depression.**
   A) True
   B) False

9. **Assessment of domestic violence victims should occur immediately after disclosure of abuse and at any follow-up appointments.**
   A) True
   B) False

10. **Florida does not presently have a toll-free domestic violence hotline, although this was a recommendation of the Governor's Task Force on Domestic Violence.**
    A) True
    B) False

Be sure to transfer your answers to the Answer Sheet insert located between pages 64–65.
PLEASE NOTE: Your postmark or facsimile date will be used as your test completion date.

Pulmonary Embolism

Audience
This course is designed for physicians, PAs, and nurses involved in assessing, triaging, and managing patients with suspected pulmonary embolism.

Course Objective
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.

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

1. Define a thromboembolic event.
2. Explain pathogenesis, risk factors, and demographics of pulmonary embolism (PE).
3. Review the diagnostic workup of PE.
4. Compare the different types of PE treatments in both inpatient and outpatient settings.

Faculty
Dalia Saha, MD, is a board-certified internal medicine physician with more than 15 years of clinical experience. With experience in both academic and private healthcare settings, Dr. Saha has vast exposure to many aspects of patient care and clinical medicine. Always interested in the didactic component of health care, Dr. Saha works on the education committee for the American College of Physicians and is an instructor and teaching staff for medical students and residents in George Washington University and Johns Hopkins Medical Schools. Lauded by her colleagues for her dedication and work ethic in the field of medicine, she has been awarded the Top Doctor Award in Washington, DC.

Faculty Disclosure
Contributing faculty, Dalia Saha, MD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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INTRODUCTION

Pulmonary embolism (PE) is very common in both inpatient and outpatient settings [1; 2]. It should be one of the first considerations when a patient presents with acute-onset dyspnea, shortness of breath, and chest pain. Other common symptoms include cough, hemoptysis, diaphoresis, and feverishness.

A PE is an abrupt occlusion of the pulmonary artery and/or one of its branches. The occlusion may consist of blood clot/thrombus, air, fat, or malignancy/tumor originating in another part of the body, which dislodges and travels through the venous system to the right side of the heart and thence the pulmonary vasculature. In most cases, PE arises from deep vein thrombophlebitis in the lower legs or pelvis, following trauma, surgery, infection, or an acquired hypercoagulable state.

The natural history of PE is variable. PE may be single or multiple (pulmonary emboli), small and clinically silent, large or recurrent with progressive obliteration of the pulmonary vascular bed, causing cardiorespiratory failure. Symptomatic PE is commonly associated with significant morbidity and mortality risk; the challenge for clinical care providers is early recognition and prompt therapeutic intervention to relieve pulmonary artery obstruction and prevent additional pulmonary emboli, any one of which could prove fatal [1; 2]. With modern technology, which can detect small embolic events, the condition is identified much earlier, making possible effective treatment prior to complete hemodynamic collapse [1; 2; 3]. Assessment and prevention in outpatient settings have also led to improvements in mortality. Research indicates that small, subclinical pulmonary emboli probably occur with some frequency but are transient in nature and go unnoticed; however,when there is predisposition to venous stasis (e.g., inflammation, injury, heart failure, coagulopathy), single large or recurrent PE becomes a challenging clinical illness requiring prompt diagnosis and treatment.

Classification of PE typically categorizes the disease as hemodynamically stable or unstable. The most common type is hemodynamically stable, which can range from small, mildly symptomatic or asymptomatic PE (previously referred to as low-risk PE or small PE) to those who present with right ventricular dysfunction but who are hemodynamically stable (previously referred to as submassive or intermediate-risk PE) [3; 4]. While PE characterized by right ventricular dysfunction can be hemodynamically stable, more severe (unstable) disease is characterized by the presence of systemic arterial hypotension, which indicates at least half of the pulmonary vascular tree is affected [4; 5]. Hemodynamically unstable PE (previously referred to as massive or high-risk PE) will result in significant hypotension. Hemodynamic instability is defined as the presence of cardiac arrest requiring resuscitation, or obstructive shock or persistent hypotension not caused by other pathologies [36].

EPIDEMIOLOGY

The annual incidence of PE is difficult to pinpoint but is estimated to be about 60 to 70 cases per 100,000 population [6]. General autopsy studies from all-cause mortality have found PE, variable in number and age, to be present in 30% to 45% of cases [6; 7; 8; 9].

Behind only stroke and coronary artery disease, PE is one of the most common types of cardiovascular disease. It is more common in patients 60 to 70 years of age, with the highest incidence in patients 70 to 80 years of age. Although death following a diagnosis of PE is relatively common, as high as 30%, many of these patients have coexisting serious conditions, such as cancer, recent surgery, or sepsis. The direct mortality associated with undiagnosed/untreated PE during the course of diagnosis and treatment is about 5% to 8%. An estimated 10% of patients with acute PE die suddenly; approximately two-thirds of patients who die from PE do so within two hours of presentation. The mortality rate for those treated for hemodynamically unstable PE is about 20%, and those with cardiogenic shock have a mortality rate of 25% to 30%. Those with a hemodynamically stable PE have a mortality rate of 1% to 25%, depending on the degree of right ventricular dysfunction [2; 4; 5; 10].

PATHOPHYSIOLOGY

Most commonly, a PE occurs when a deep vein thrombus detaches and migrates, or embolizes, into the pulmonary circulation. This can lead to blockage of the pulmonary vasculature, causing a ventilation-perfusion (VQ) mismatch and impairing gas exchange and circulation. PE is more common in the lower lung fields, compared with the upper ones, and both lungs are typically involved. Peripheral PE, as opposed to central PE, can lead to a pulmonary infarction coupled with alveolar hemorrhage. As further obstruction of the pulmonary artery occurs, there is an increase in dead space ventilation and elevation of pulmonary arterial pressure by increasing pulmonary vascular resistance. This further worsens VQ mismatch, with vascular occlusion of the arteries.

Various serum factors are released during a PE formation, including serotonin and thromboxane, which are produced from activated platelets [1; 2; 4]. This induces a cascade of hormonal triggers and related vasoconstriction. Pulmonary arterial pressure increases, which worsens right ventricular afterload and can lead to right ventricular failure and eventually left ventricular system failure. Further clinical progression will lead to a myocardial ischemia due to inadequate coronary circulatory flow, systemic hypotension, and eventual death [1; 4; 5].

DIAGNOSIS

A strict (confirmatory) diagnosis of PE would require direct anatomic evidence of pulmonary artery obstruction, which by modern imaging technique (e.g., computed tomography [CT] angiography) would involve invasive measures and exposure to radiation. As the size and distribution (severity) of PE are variable, the preferred strategy for selecting diagnostic testing relies on degree of clinical suspicion, clinical judgment, and assessment of pre-test probability. Selection of noninvasive testing to rule out the diagnosis, based on the assessed clinical probability of PE, has proved effective in reducing the use of CT imaging, thereby minimizing lung and breast-tissue exposure to irradiation [27]. The differential diagnosis includes heart failure, pneumothorax, pneumonia, sepsis, acute chest syndrome, chronic obstructive pulmonary disease (COPD) exacerbation, and anxiety or other psychotropic illnesses. A systematic review and meta-analysis found that a history of sudden dyspnea, syncope, thrombophlebitis, previous deep vein thrombosis, leg swelling, active cancer, or recent surgery was associated with an increased probability of PE [54]. An inability to increase alveolar oxygen pressure (PaO_2) greater than 8.0 kPa (60 mm Hg) despite high-flow oxygen should also raise suspicion for PE.

When a patient does not speak the same language as the clinician, a professional interpreter should be consulted to ensure accurate communication. A retrospective chart review found that, for non-English-speaking patients suspected of having sustained a PE, the positive diagnostic yield of pulmonary angiogram for those who requested an interpreter (7.37%) was nearly double that of those who did not request an interpreter (3.23%) [49].

DIAGNOSTIC WORKUP

Vital Signs

In initial evaluation, vital signs such as blood pressure, heart rate, and rapid estimation of oxygenation by pulse oximetry are critical to assessing severity of vascular compromise and the stability of the patient. Arterial blood gas (ABG) testing will confirm if a patient has hypoxemia and can be used to obtain the arterial-alveolar gradient to determine if there is a PE or other VQ mismatch [10; 11; 12; 13].

D-dimer Level

Assessment of D-dimer levels can be used for screening purposes and to rule out PE if the pretest probability is intermediate or low. D-dimer is a byproduct of intrinsic fibrinolysis. It is considered to be a highly sensitive test for the absence of PE and has a very high negative predictive value. A normal D-dimer level effectively rules out PE or deep vein thromboembolism. In the event that the d-dimer is elevated, further testing (e.g., computed tomography [CT] angiography, planar VQ scanning) can be performed [10; 14; 15; 16]. Because the

MODIFIED PROSPECTIVE INVESTIGATION OF PULMONARY EMBOLISM DIAGNOSIS (PIOPED-II) CRITERIA	
Probability of PE	**Criteria**
High probability	Two or more large mismatched segmental perfusion defects or the arithmetic equivalent of moderate and/or large defects
Normal perfusion or very low probability	No perfusion defects Nonsegmental perfusion defects without other perfusion defects in either lung Perfusion defects smaller than corresponding chest x-ray opacity One to three small subsegmental perfusion defects Two or more matched ventilation and perfusion defects with a regionally normal chest x-ray and some areas of normal perfusion elsewhere Solitary triple-matched defect in a single segment in the middle or upper lung zone Stripe sign Large pleural effusion without other perfusion defects in either lung
Low or intermediate probability	All other findings
Source: [19]	*Table 1*

test is not specific, an elevated finding is not diagnostic. The specificity of D-dimer decreases with age, and the use of age-adjusted cut-offs is recommended for patients older than 50 years of age. The formula is age (years) x 10 mcg/L for patients older than 50 years of age.

Cardiac Biomarkers

Cardiac biomarker testing may also be useful, particularly as it can identify other diagnoses (e.g., myocardial infarction) [10; 11; 17]. It may help identify signs of right ventricular strain and/or ischemia. An elevated brain natriuretic peptide (BNP) level may indicate right ventricular dysfunction, and higher levels correlate with greater severity of dysfunction.

Various cardiac troponins have also been assessed for diagnostic significance in patients with PE. While these measurements are not diagnostic, elevated troponin is significantly associated with higher mortality in patients with PE [18].

Imaging

Diagnostic imaging is indicated for patients in whom PE cannot be ruled out based on clinical assessment and noninvasive testing. For these patients, CT pulmonary angiography is usually an easily accessible diagnostic imaging modality. It is fast, accurate, and both specific and sensitive. It is also useful for identifying other lung pathology, such as pneumonia and effusions [15; 16]. However, it does require that the patient have good renal function due to the use of iodinated contrast, and it also entails lung and breast-tissue irradiation. Ventilation-perfusion single-photon-emission CT (VQ scan) is a low-radiation option to minimize radiation exposure in younger patients.

Chest x-ray is nonspecific but can help identify pleural effusions and diaphragmatic changes. The classic Westermark sign, which shows a clarified area (loss of vascular markings) distal to a large occluded vessel, and Hampton hump, a dome-shaped, pleural-based opacification, may be present on x-ray. These findings are strongly specific for PE (92% and 82%, respectively) but are not sensitive (14% and 22%, respectively). Chest x-ray can also assist in ruling out pneumonia as part of the differential.

VQ scans visualize areas that are ventilated but not perfused (i.e., VQ mismatch). This testing requires more time, is less specific than CT angiography, and should be done with clinical correlation. However, it is the imaging modality of choice for patients with suspected PE and normal chest x-ray for whom CT angiography is contraindicated, including those with impaired kidney function and pregnant patients. Normal ventilation is 4 L air/minute, and normal perfusion is 5 L blood/minute; thus, a normal VQ ratio is 0.8. A high VQ ratio (>0.8) indicates that the patient's ventilation is exceeding perfusion, while a low VQ ratio indicates a VQ mismatch caused by poor ventilation. When blood is diverted away from the occluded section, overperfusion can occur in the normally ventilated regions. The modified Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED-II) criteria score the probability of PE based on VQ scan findings (***Table 1***).

Duplex ultrasonography for detection of lower extremity venous thrombi is a useful noninvasive test to assess risk and probability in a patient suspected of having PE. It has both high sensitivity and specificity for thrombus [14; 20; 21; 22]. However, a negative test result does not rule out PE, as the thrombus may have dislodged and embolized prior to the testing.

Electrocardiogram

Electrocardiographic signs of right ventricle strain, such as T wave inversions in V1–V4, QR pattern in V1, the S1Q3T3 pattern, and incomplete or complete right bundle-branch block, are useful but insensitive for the assessment of right ventricle dysfunction in acute PE. However, the presence of right ventricular strain on electrocardiogram has been shown to correlate with the extent of pulmonary vascular obstruction and outcomes of acute PE [10; 11; 12; 14; 17; 24].

Echocardiogram

Echocardiography can demonstrate if there was a clot in the right atrium or ventricle and can also be used to show if there are signs of right ventricular dilatation and hypokinesis [12]. When performed, echocardiography has been shown to reduce other testing and lead to more aggressive early therapy [12; 22].

Pulmonary Arteriography

Pulmonary arteriography is a rare test typically performed only on patients with suspected PE for whom CT and chest x-ray are not feasible. It may also be used with cardiac catheterization to assess patients who have chronic thromboembolic pulmonary hypertension to determine if they are good candidates for pulmonary endarterectomy.

GENETIC TESTING

Factor V Leiden (FVL) and prothrombin (PT) genetic variants are associated with an increased risk of future venous thrombosis or PE. Genetic tests for FVL and PT variants are widely available and commonly used. One current use of these tests is to inform decisions regarding anticoagulant medication in order to decrease the risk of future clots (i.e., secondary prevention). The independent Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group found enough evidence to recommend against routine testing for FVL and PT gene variants in adults who have idiopathic venous thromboembolism, since longer term preventive treatment with anticoagulant medication offers similar benefits to patients whether or not they have these genetic variations. They also recommend against routine testing for adult family members who do not have a history or symptoms of venous thromboembolism, when the testing is conducted to help decide whether to treat them preventively with anticoagulant medication [50]. However, for patients with venous thromboembolism associated with commonly recognized modifiable risk factors (e.g., contraceptive use, estrogen replacement), genetic testing may help guide preventive treatment decisions.

CLINICAL SCORING SYSTEMS

The Wells criteria (***Table 2***) and the PE Rule-Out Criteria (PERC) assist clinicians with determining clinical probability for PE [14]. One of the important criteria in the determination of PE is if there is a more likely alternate diagnosis, and this is somewhat subjective. If the Wells criteria are used, a score greater than 6 is considered high probability of PE, 2–6 is moderate probability, and less than 2 is low probability. A modification of the Wells criteria simplifies scoring to either likely (>4) or unlikely (≤4).

WELLS CRITERIA

Clinical Features	Points
Clinical symptoms of deep vein thromboembolism	3
Other diagnosis less likely than PE	3
Tachycardia (>100 beats per minute)	1.5
Immobilization for three or more days OR surgery in the past four weeks	1.5
Previous deep vein thromboembolism or PE	1.5
Hemoptysis	1
Malignancy	1

Source: [25] *Table 2*

The PERC rule was developed for use in emergency care to rule-out PE in patients whose likelihood of PE is low (<15%), so unnecessary diagnostic workups can be avoided. The PERC rule includes [26]:

- Age younger than 50 years
- Heart rate less than 100 beats per minute
- Oxygen saturation of at least 95%
- No prior deep vein thrombosis or PE
- No unilateral leg swelling
- No hormonal estrogen use
- No hemoptysis
- No history of surgery or trauma requiring prior hospitalization in the previous four weeks

If all eight criteria are fulfilled, the patient's risk for PE can be considered sufficiently low and further testing is not necessary [10; 11; 13; 17]. In practice, clinicians tend to overestimate the probability of PE. In cases in which the clinician judges that the patient is very unlikely to have PE but is uncertain whether the estimated likelihood is <15%, the PERC rule or Wells score ≤4 in combination with a normal D-dimer level is reassuring and can be used to safely rule out PE.

TREATMENT

INITIAL MANAGEMENT

The mainstays of initial PE management focus on rapid assessment of clinical severity and stabilization of the patient. As noted, when a patient initially presents, the most critical pieces of information lie in their vital signs (e.g., heart rate, blood pressure, oxygenation). The initial goal for the patient with PE is to maintain oxygen levels. If mechanical circulatory support

is required, cardiopulmonary bypass permits right ventricular recovery by decompressing the dilated and dysfunctional ventricle through diversion of the cardiac output to a pump and oxygenator [51]. Alternatively, venoarterial extracorporeal membrane oxygenation (VA-ECMO) functions similarly but is more mobile, allowing for support to be initiated and continued in more diverse settings.

For patients who are hemodynamically unstable, intravenous fluid should be given with caution, because this can lead to right ventricular overload. Hemodynamically stable, low-risk patients should receive anticoagulation alone; those who are at high risk and have hemodynamic compromise may require systemic thrombolysis or surgical- versus catheter-directed therapy. Those who are at intermediate risk have more complicated cases and can be treated with either anticoagulation alone or anticoagulation with potential procedures. As discussed, the risk level will depend on the severity of right ventricular dysfunction on echocardiography, the degree of troponin elevation, the amount of oxygen and vasopressor required, and clot burden and location [10; 11; 12; 13]. The American Society of Hematology (ASH) recommends that patients with PE at low risk for complications be offered home treatment rather than hospital treatment [27].

The therapeutic treatment strategy for patients with a new diagnosis of PE, and venous thromboembolism in general, can be divided into three phases: initial treatment (the first three weeks after diagnosis), primary treatment (three to six months, or longer), and secondary prevention (beginning upon completion of primary therapy and continuing indefinitely) [27]. For primary treatment of patients with PE, whether unprovoked or provoked by a transient or chronic risk factor, the ASH suggests a shorter course of anticoagulation therapy (3 to 6 months) be preferred over a longer course (6 to 12 months). Anticoagulation therapy may be continued indefinitely in select patients for whom the risk for bleeding complications is less than the risk of recurrent PE.

PRIMARY PHARMACOTHERAPY

In selecting initial pharmacotherapy, European guidelines and a 2022 clinical practice review recommend that treatment be guided by risk stratification of PE as high, intermediate, or low based on the patient's clinical presentation [36; 55]. Approximately 5% of patients present with signs of high-risk PE (e.g., shock, end-organ hypoperfusion/dysfunction, blood pressure <90 mm Hg) not caused by arrhythmia, hypovolemia, or intrinsic heart failure [55]. Intermediate-risk patients are those who present with echocardiographic evidence of right heart strain, elevated cardiac biomarkers, or both; those who are hemodynamically stable with normal cardiac biomarkers and no evidence of right ventricular strain are classified as having low-risk PE. Patients classified as having high-risk PE are candidates for initial reperfusion (thrombolytic) therapy; those with intermediate- and low-risk PE should receive immediate anticoagulation therapy [36; 55]. Treatment should be started promptly whenever PE is strongly suspected and the patient's risk of serious bleeding complications is low. Pharmacotherapy options for initial anticoagulation include intravenous unfractionated heparin, subcutaneous low-molecular-weight heparin, subcutaneous fondaparinux, factor Xa inhibitors (e.g., apixaban, rivaroxaban), direct thrombin inhibitors (e.g., dabigatran), and intravenous argatroban for patients with heparin-induced thrombocytopenia.

Thrombolytic Therapy

Patients who present with high-risk PE warrant consideration for immediate reperfusion therapy, there being no contraindications (e.g., brain metastases, bleeding disorders, recent surgery) [36; 55]. Intravenous systemic thrombolysis is a readily available option for reperfusion. Thrombolytic agents act to dissolve the thrombus by converting plasminogen into plasmin. With early thrombus resolution, the elevated pulmonary arterial pressure/resistance and accompanying right ventricular dysfunction improve rapidly. Thrombus resolution within the first 24 hours in particular is much faster in thrombolytic therapy than with heparin [52].

The first recombinant tissue plasminogen activator, and the most commonly used thrombolytic agent used in patients with PE, is alteplase (rtPA); other available agents include streptokinase, urokinase, reteplase, and tenecteplase. The main indication for thrombolysis is high-risk PE with thrombus and hemodynamic instability. rtPA is administered at a rate of 50 mg per hour for two hours; the dose should be reduced for patients with weight less than 65 kg. If streptokinase, is used, a loading dose of 250,000 IU is given, followed by and infusion of 100,000 IU per hour for 24 hours. Urokinase is started with a loading dose of 4,400 IU and an infusion of 4,400 IU/kg/hour for 12 hours [29; 52].

According to the American College of Physicians, catheter-directed thrombolytic therapy can be considered if cardiopulmonary deterioration is imminent [53]. There is some evidence that ultrasound-assisted catheter-directed thrombolysis is superior to heparin anticoagulation alone in improving right ventricular dilatation within 24 hours without major bleeding complications or recurrent embolism. Absolute contraindications to thrombolytic therapy include history of intracranial hemorrhage, known structural cerebral vascular lesion, known malignant intracranial neoplasm, recent history (within past three months) ischemic stroke, active bleeding (excluding menses), and recent history (within past three months) significant closed-head trauma or facial trauma [52; 53].

Oral Anticoagulants

Direct oral anticoagulants (DOACs) (factor Xa inhibitors or direct thrombin inhibitors) are recommended over vitamin K antagonists (e.g., warfarin) for most patients; however, those with renal insufficiency (i.e., creatinine clearance <30 mL/min), moderate-to-severe liver disease, or antiphospholipid syndrome are not good candidates for DOAC therapy [27].

ORAL ANTICOAGULATION THERAPY	
Agent	**Dosage**
Vitamin K Antagonist	
Warfarin	5 mg once daily for most patients[a]
Direct Thrombin Inhibitor	
Dabigatran etexilate	After at least 5 days of initial therapy with a parenteral anticoagulant, transition to oral 150 mg twice daily.
Factor Xa Inhibitors	
Apixaban	10 mg twice daily for 7 days, followed by 5 mg twice daily
Edoxaban	After at least 5 days of initial therapy with a parenteral anticoagulant, transition to once-daily oral 60 mg for patients >60 kg or 30 mg for patients ≤60 kg.
Rivaroxaban	15 mg twice daily with food for 21 days, followed by 20 mg once daily with food
[a]For patients who are expected to be more sensitive to warfarin, a starting dose of 2.5 mg daily is recommended. After three days of treatment, dosage should be adjusted based on INR values.	
Source: [29]	*Table 3*

EVIDENCE-BASED PRACTICE RECOMMENDATION

The European Society of Cardiology (ESC) and European Respiratory Society (ERS) recommends direct oral anticoagulants (DOACs) as first choice anticoagulants over warfarin even in those who are warfarin eligible.

(https://academic.oup.com/eurheartj/article/41/4/543/5556136. Last accessed August 18, 2023.)

Level of Evidence: Expert Opinion/Consensus Statement

Factor Xa inhibitors such as apixaban and rivaroxaban have the advantage of fixed dosing and no need for monitoring laboratory values, both of which are required of vitamin K antagonists. Rivaroxaban and apixaban do not require any kind of overlap with an intravenous agent. Dose reductions are indicated for those with renal insufficiency. Apixaban can be used in patients with renal insufficiency and is safe for patients on dialysis [2; 28]. Reversal agents are available: idarucizumab for reversal of dabigatran, and andexanet alfa for apixaban and rivaroxaban.

The half-life of factor Xa inhibitors is much shorter than the half-life of warfarin. If bleeding develops and requires reversal, a four-factor prothrombin complex concentrate can be used. Direct thrombin inhibitors such as dabigatran can also be used for treatment for these patients. For those with heparin-induced thrombocytopenia, intravenous argatroban or subcutaneous fondaparinux can be used for anticoagulation. The dosage varies according to agent (***Table 3***).

Drug-drug interactions with DOACs are common and may increase risk of bleeding or thrombosis. Important DOAC interactions are often due to medications that affect cytochrome P450 (CYP450) enzymes or transport proteins or increase bleeding propensity.

Warfarin, which used to be the mainstay of therapy, is no longer considered first choice, as the other DOACs have better safety profiles and patient satisfaction. Bleeding is common with warfarin usage and is more likely to be develop in patients who are older (65 years of age and older) and with comorbidities, such as diabetes, recent myocardial infarction, and other chronic conditions (e.g., kidney disease, stroke). If it develops, bleeding can be reversed with vitamin K at a dose of 2.5–10 mg intravenously or orally. Fresh frozen plasma can also be used with elevated prothrombin complex concentrates [5; 30; 31]. Drug interactions are also a concern with warfarin. Another potential complication is warfarin-induced necrosis, which is more likely to occur in patients with a history of heparin-induced thrombocytopenia. If warfarin is used, the dose should be adjusted to reach and maintain a target goal of an international normalized ratio (INR) of 2.5 (range: 2.0–3.0).

Heparin

Intravenous unfractionated heparin has a short half-life and can be reversed with protamine [28]. An initial bolus is given followed by an infusion, during which partial thromboplastin time (PTT) values are monitored. The dosage is based on a weight-based protocol. Although relatively safe to use, the pharmacokinetics of this drug are unpredictable, resulting in the need for close clinical monitoring. However, due to its short half-life, it can quickly be reversed, if needed.

Subcutaneous low-molecular-weight heparin has several advantages, including increased bioavailability and more predictable anticoagulation, as opposed to intravenous unfractionated heparin [28; 32]. There is also decreased incidence of bleeding and potentially better outcomes. Low-molecular-weight heparin is given at a dosage of 1 mg/kg body weight. All heparin products include similar bleeding risk profiles as well as a risk

for thrombocytopenia, urticaria, and anaphylaxis. For patients with breakthrough deep vein thrombosis and/or PE during therapeutic warfarin treatment, the ASH suggests using low-molecular-weight heparin over DOAC therapy [27].

Fondaparinux

Fondaparinux is a factor Xa antagonist given subcutaneously in the management of acute PE instead of heparin. Advantages include fixed-dose administration once or twice per day, lack of need for clinical monitoring, and lower risk of thrombocytopenia. The dose is 5 mg for patients who weigh less than 50 kg, 7.5 mg for patients weighing 50–100 kg, and 10 mg for those weighing more than 100 kg. The dose should be adjusted in persons with kidney disease. It is contraindicated for patients with a creatinine clearance less than 30 mL/minute. When used for thromboprophylaxis, some experts recommend a 50% dose reduction or use of low-dose heparin instead [29].

SURGICAL MANAGEMENT

Pulmonary embolectomy is indicated for patients that have high- or intermediate-risk PE with contraindications to thrombolysis; failed thrombolysis or catheter-assisted embolectomy; or hemodynamic shock that is likely to cause death before thrombolysis can take effect [52]. Surgical pulmonary embolectomy is a procedure performed on cardiopulmonary bypass through a midline sternotomy, involving either central or femoral vessel initiation. Management involves moderate hypothermia for better visualization and protection during moments of reduced cardiopulmonary bypass flows. Aortic cross-clamping and cardioplegic arrest are sometimes unnecessary to prevent negative effects on right ventricular recovery [51]. Dual incisions offer improved visualization and better clot extraction. Various methods, such as suction, retrograde perfusion, manual manipulation, or balloon-tipped catheters, can aid clot extraction, but balloon catheters may lead to increased postprocedural complications [51].

SECONDARY PREVENTION

Maintenance anticoagulation for secondary prevention is done for patients who have extensive clot burden or to reduce the risk of new clot formation. There are multiple pharmacotherapeutic options for this phase of treatment, including factor Xa inhibitors (e.g., apixaban), dabigatran, and aspirin. Warfarin and low-molecular-weight heparin are second-line options.

Factor Xa anticoagulants, such as apixaban and rivaroxaban, are the most common first-line option for secondary prevention. Though warfarin was previously used, research has shown a decreased risk for intracranial hemorrhage with factor Xa anticoagulants compared with warfarin. When used for maintenance therapy, the dosage of apixaban is 2.5 mg twice per day; the dosage of rivaroxaban is 10 mg once per day. Cessation of therapy should be considered again after 6 to 12 months [4; 5].

Those with incidental PE, very small clot burdens, and minimal symptoms should likely be treated in an outpatient setting—unless other risk factors are present. However, patients with hemodynamically unstable PE (e.g., extensive clot burden, low blood pressure, abrupt clinical deterioration) often require an intensive care stay.

Aspirin has also been studied for long-term maintenance therapy and is more effective than placebo. However, anticoagulation is typically preferred over aspirin. When anticoagulation therapy is initiated in patients with PE with stable cardiovascular disease who were previously taking aspirin for cardiovascular risk modification, clinicians should consider suspending the aspirin during anticoagulation therapy. Enoxaparin sodium or low-molecular-weight heparin may be used in high-risk cancer patients with recurrent PE [2; 28].

Duration of Pharmacotherapy for Secondary Prevention

As noted, the duration of anticoagulation therapy for secondary prevention is dependent on a variety of factors, such as bleeding risk and risk factors for PE, and can range from three months to lifelong therapy [3; 28; 32]. If the patient experienced PE following a transient risk factor (i.e., a provoked event), such as immobilization or recent surgery or trauma, at least three months of treatment is warranted, after which therapy should be reassessed. However, those who have chronic provoked factors for PE, such as active cancer, a hypercoagulable state, or chronic immobility, may benefit from long-term (indefinite) anticoagulation therapy. When creating the treatment plan, the goal is to weigh the benefits of PE and deep vein thrombosis prevention with the risk of anticoagulation events (e.g., bleeding). Risk factors for bleeding include age 65 years or older, frequent falls, alcohol abuse, renal failure, previous stroke, diabetes, and anemia.

For patients who develop PE provoked by a transient risk factor and who have a history of a previous thrombotic event also provoked by a transient risk factor, the ASH guideline panel suggests stopping anticoagulation after completion of the primary treatment phase of therapy [27].

PE IN THE OUTPATIENT SETTING

When possible, patients at assessed low risk for complications (i.e., minimal risk of PE-related death) should be discharged from the hospital and continue to receive treatment at home. Such patients are hemodynamically stable, with have no right heart strain and normal cardiac biomarkers. Most patients with low-risk PE can be treated with an oral anticoagulant or a brief period of low-molecular-weight heparin followed by oral therapy. The presence or absence of comorbidities and proper care and anticoagulation therapy, which can be provided on an outpatient basis, should be noted. Scoring systems have been developed to stratify these patients, including the HESTIA rule (***Table 4***), the PE Severity Index (PESI), and its simplified version (sPESI) (***Table 5***) [33; 34; 35].

The PESI scales identify those with a low risk of 30-day mortality [33]. The criteria used include age, sex, history of cancer, history of chronic pulmonary disease, heart rate, systolic blood pressure, and oxygen saturation [33]. The scales relate

HESTIA EXCLUSION CRITERIA FOR OUTPATIENT TREATMENT	
Criteria	**Points[a]**
Hemodynamically unstable	1
Thrombolysis or embolectomy needed	1
Active bleeding or high risk of bleeding	1
More than 24 hours on supplemental oxygen needed to maintain oxygen saturation >90%	1
PE diagnosed during anticoagulant treatment	1
Severe pain requiring IV pain medication for more than 24 hours	1
Medical or social reason for hospital treatment for more than 24 hours (e.g., infection, malignancy, no support system)	1
Creatinine clearance of <30 mL/min	1
Severe liver impairment	1
Pregnancy	1
History of heparin-induced thrombocytopenia	1
[a]A score of 1 or more is defined as high risk and rules out outpatient treatment.	
Source: [36]	*Table 4*

THE ORIGINAL PULMONARY EMBOLISM SEVERITY INDEX (PESI) AND THE SIMPLIFIED PESI (sPESI) CLINICAL RISK SCORES		
Parameter	**PESI**	**sPESI**
Age	Age in years	1 if older than 80 years
Male sex	10	—
Cancer diagnosis	30	1
Chronic heart failure Chronic pulmonary disease	10 10	1
Pulse ≥110 beats per minute	20	1
Systolic blood pressure <100 mm Hg	30	1
Respiratory rate ≥30 breaths per minute	20	—
Temperature <36°C	20	—
Altered mental status	60	—
Arterial oxyhemoglobin saturation <90%	20	1
Risk Stratification (PESI)		
Class I (≤65 points)	Very low 30-day mortality risk (0% to 1.5%)	
Class II (66–85 points)	Low mortality risk (1.7% to 3.5%)	
Class III (86–105 points)	Moderate mortality risk (3.2% to 7.1%)	
Class IV (106–125 points)	High mortality risk (4% to 11.4%)	
Class V (>125 points)	Very high mortality risk (10% to 24.5%)	
sPESI Score		
0 points	30-day mortality risk 1%	
1 or more points	30-day mortality risk 10.9%	
Source: [37; 56; 57]		*Table 5*

the risk stratification score to an associated 30-day mortality and risk of death and can assist in identifying patients who may appropriately be managed at home. The patient's social situation, access to supportive care, and ability to transfer to higher level care should all be considered before shifting to outpatient management.

Anticoagulation options to manage confirmed PE in an outpatient setting include subcutaneous low-molecular-weight heparin, fondaparinux, unfractionated heparin, or DOACs [28; 32; 38; 39]. The treatment duration is generally three to six months [38; 39]. Following the initial three-month period, the decision of whether or not to continue treatment will be made based on continued risk of recurrent thromboembolic balanced against the risks of continued anticoagulation [4; 5; 40].

PE AND COVID-19

Hospitalized patients with advanced COVID-19 may have laboratory signs of a coagulopathy and increased risk for arterial and venous thromboembolic complications, including PE [41; 42; 43]. The pathogenesis is unknown but likely involves some combination of systemic inflammation, endothelial dysfunction, platelet activation, immobility, and stasis of blood flow [43]. The earliest abnormalities are elevated D-dimer levels and mild thrombocytopenia; with disease progression, fibrin degradation products are elevated and prothrombin time becomes prolonged. Laboratory measure of coagulation factors in patients hospitalized with COVID-19 provides a way to track disease severity. The presence of an elevated D-dimer on admission carries a poor prognosis and has been associated with increased risk of requiring mechanical ventilation, intensive care unit admission, and mortality [43; 44]. The most frequently reported complications of COVID-19 coagulopathy are deep venous thrombosis and PE. In a prospective study of 150 critically ill patients from two centers in France, 25 patients developed PE and 3 developed deep vein thrombosis, despite prophylactic anticoagulation [45]. In a report of 184 patients with severe COVID-19 from three centers in the Netherlands, the cumulative incidence of venous thromboembolism was 27%, including PE in 80% of the cases affected [46]. Other centers have reported lower rates. Among 393 patients from New York, venous thromboembolism was diagnosed in only 13 patients (3.3%), 10 of whom were on mechanical ventilation [47]. The National Institutes of Health recommends all hospitalized patients with COVID-19 who experience rapid deterioration of pulmonary, cardiac, or neurological function or sudden, localized loss of peripheral perfusion be evaluated for thromboembolic disease [48].

At present, there are limited data available to inform clinical management around prophylaxis or treatment of venous thromboembolic complications in patients with COVID-19 [41]. One source of interim guidance recommends regularly monitoring hemostatic markers—namely D-dimer, prothrombin time, and platelet count—in all patients presenting with COVID-19 and prophylactic use of low-molecular-weight heparin in all hospitalized patients, unless there are contraindications [43]. The National Institutes of Health recommends that hospitalized, nonpregnant adults with COVID-19 who do not require intensive-level care and have no evidence of venous thromboembolism receive a therapeutic dose of heparin if their D-dimer levels are above the upper normal limit and they require low-flow oxygen, as long as they do not have an increased risk of bleeding [48].

Contraindications for the use of therapeutic anticoagulation in patients with COVID-19 include [48]:

- Platelet count <50 x 10^9/L
- Hemoglobin <8 g/dL
- Need for dual antiplatelet therapy
- Bleeding within the past 30 days that required an emergency department visit or hospitalization
- History of a bleeding disorder or an inherited or active acquired bleeding disorder

Low-molecular-weight heparin is preferred over unfractionated heparin because of its ease of administration and because low-molecular-weight heparin was the predominant form of heparin used in the clinical trials for COVID-19 [48].

In patients without venous thromboembolism who have started treatment with therapeutic doses of heparin, treatment should continue for 14 days or until they are transferred to intensive care or discharged from the hospital, whichever comes first. A prophylactic dose of heparin is also recommended for patients who do not meet the criteria for receiving therapeutic heparin or are not receiving a therapeutic dose of heparin for other reasons, unless a contraindication exists [48].

For those patients who develop a PE in the setting of a COVID-19 infection, about 50% will report persistent fatigue, reduced exercise tolerance, and dyspnea [14; 23]. Of these patients, one-half will also have signs of right ventricular dysfunction on echocardiogram after the diagnosis is made, referred to as post-PE syndrome. This further leads to dyspnea on exertion, damage to the venous valves in the leg, prolonged lower extremity swelling and aching, venous ulcers, and impaired quality of life.

CONCLUSION

PE is a common cause of acute-onset breathlessness and chest pain, often confused for many other diagnoses. It should remain on one's clinical differential due to the fact that it can be life-threatening and is treatable if caught and managed early. A variety of treatment options are at the forefront for ensuring that patients are given the best possible outcome.

Customer Information/Answer Sheet/Evaluation insert located between pages 64–65.

COURSE TEST
#90120 PULMONARY EMBOLISM

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 2 credit activity must be completed by August 31, 2026.

1. Classification of pulmonary embolism (PE) typically categorizes the disease as
- A) *left or right.*
- B) *acute or chronic.*
- C) *massive or supermassive.*
- D) *hemodynamically stable or unstable.*

2. The annual incidence of PE is difficult to pinpoint but is estimated to be about
- A) *6 to 7 cases per 100,000 population.*
- B) *26 to 37 cases per 100,000 population.*
- C) *60 to 70 cases per 100,000 population.*
- D) *160 to 170 cases per 100,000 population.*

3. The majority of patients who die from PE do so
- A) *within 60 minutes of presentation.*
- B) *within two hours of presentation.*
- C) *after more than two days of treatment.*
- D) *more than two weeks after presentation.*

4. Most commonly, a PE occurs when
- A) *a portion of a malignant tumor enters into the pulmonary circulation.*
- B) *a deep vein thrombus detaches and embolizes into the pulmonary circulation.*
- C) *nitrogen bubbles form in the blood vessels and embolize into the pulmonary circulation.*
- D) *air enters the systemic venous circulation and travels to the right ventricle and pulmonary circulation.*

5. The differential diagnosis of PE includes all of the following, EXCEPT:
- A) *Pneumonia*
- B) *Heart failure*
- C) *Pneumothorax*
- D) *Hyperthyroidism*

6. Which of the following statements regarding D-dimer testing in patients with suspected PE is TRUE?
- A) *A normal D-dimer level effectively rules out PE.*
- B) *Assessment of D-dimer levels should never be used for screening.*
- C) *In the event that the D-dimer is low, planar VQ scanning is essential.*
- D) *The specificity of D-dimer increases with age and is most useful in patients older than 50 years of age.*

7. What is the imaging modality of choice when evaluating patients with suspected PE and normal chest x-ray for whom CT angiography is contraindicated?
- A) *MRI*
- B) *A VQ scan*
- C) *Ultrasound*
- D) *Fluoroscopy*

8. In the primary management of PE, the dose of apixaban is
- A) *5 mg once daily for most patients.*
- B) *10 mg twice daily for seven days, followed by 5 mg twice daily.*
- C) *15 mg twice daily with food for 21 days, followed by 20 mg once daily with food.*
- D) *once-daily oral 60 mg for patients who weigh more than 60 kg or 30 mg for patients 60 kg of less.*

9. Patients who have chronic provoked factors for PE, such as active cancer, a hypercoagulable state, or chronic immobility, should continue anticoagulation therapy

A) for three months.
B) for six months.
C) for one year.
D) indefinitely.

10. According to the HESTIA exclusion criteria, a patient with which of the following would be ineligible for outpatient PE treatment?

A) Pregnancy
B) PE diagnosed during anticoagulant treatment
C) Severe pain requiring IV pain medication for more than 24 hours
D) Any of the above

Be sure to transfer your answers to the Answer Sheet insert located between pages 64–65.
PLEASE NOTE: Your postmark or facsimile date will be used as your test completion date.

Strategies for Appropriate Opioid Prescribing: The Florida APRN/PA Requirement

This course meets the Florida requirement for 3 hours of Controlled Substance education.

Audience

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

Faculty

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

Faculty Disclosure

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

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

Senior Director of Development and Academic Affairs

Sarah Campbell

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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 2010 with both now in multi-year decline, but information on these important trends is largely absent in the medical literature and media reporting.

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.

DEFINITIONS

Definitions and use of terms describing opioid analgesic misuse, abuse, and addiction have changed over time, and their current correct use is inconsistent not only among healthcare providers, but also by federal agencies reporting epidemiologic data such as prevalence of opioid analgesic misuse, abuse, or addiction. Misuse and misunderstanding of these concepts and their correct definitions have resulted in misinformation and represent an impediment to proper patient care.

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 pseudo-addiction. 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]. For example, a 2013 survey measuring 200 primary care physicians' understanding of opioids and addiction found that [3]:

- 35% admitted knowing little about opioid addiction.
- 66% and 57% viewed low levels of education and income, respectively, as causal or highly contributory to opioid addiction.
- 30% believed opioid addiction "is more of a psychologic problem," akin to poor lifestyle choices rather than a chronic illness or disease.
- 92% associated prescription analgesics with opioid addiction, but only 69% associated heroin with opioid addiction.
- 43% regarded opioid dependence and addiction as synonymous.

This last point is very important because confusion and conflation of the clinical concepts of dependence and addiction has led to accusations of many non-addicted patients with chronic pain of misusing or abusing their prescribed opioid and in the failure to detect treatment-emergent opioid problems [4]. Knowledge gaps concerning opioid analgesics, addiction, and pain are related to attitude gaps, and negative attitudes may interfere with appropriate prescribing of opioid analgesics. For example, when 248 primary care physicians were asked of their prescribing approach in patients with headache pain with either a past or current history of substance abuse, 16% and 42%, respectively, would not prescribe opioids under any circumstance [5]. Possibly contributing to healthcare professionals' knowledge deficit in pain treatment is the extent of educational exposure in school. A 2011 study found that U.S. medical school students received a median seven hours of pain education and Canadian medical students a median 14 hours, in contrast to the median 75 hours received by veterinarian school students in the United States [6]. Additionally, less than 3% of medical schools incorporate pain management into their curriculum, yet chronic pain is the most common reason patients see a provider, accounting for 40% of all visits in primary care [7].

The terms related to addiction are often inconsistent, inaccurate, and confusing, partially reflecting the diverse perspectives of those working in the related fields of health care, law enforcement, regulatory agencies, and reimbursement/payer organizations. Changes over time in the fundamental understanding of addiction have also contributed to the persistent misuse of obsolete terminology [8]. The *Diagnostic and Statistical Manual of Mental Disorders* (DSM), published by the American Psychiatric Association, is the standard reference for the diagnosis of addiction and all other psychiatric disorders. Prior to the 2013 release of the DSM-5, versions of the DSM eschewed the term "addiction" in favor of "substance dependence," with a separate diagnostic entity of "substance abuse" representing a less severe version of dependence [9]. Also, in earlier DSM versions, physiologic dependence, manifesting as substance tolerance and withdrawal, was considered a diagnostic criterion of substance dependence. The result was the perpetuation of patient and healthcare professional confusion between physical and substance dependence and the belief that tolerance and withdrawal meant addiction. This confusion also enhanced provider and patient fears over addiction developing from opioid analgesics and contributed to the undertreatment of pain. The DSM-5 has eliminated substance dependence and substance abuse by combining them into the single diagnostic entity of substance use disorder. The disorder is measured on a continuum from mild to severe [9].

In 2011, the American Society of Addiction Medicine (ASAM) published their latest revision in defining the disease of addiction. Owing to the increased public understanding and acceptance of addiction as a chronic brain disease, ASAM published an updated definition of addiction in 2019, with the goal of making it more accessible to patients, the media, and policy makers. The updated definition states that [10]:

> Addiction is a treatable, chronic medical disease involving complex interactions among brain circuits, genetics, the environment, and an individual's life experiences. People with addiction use substances or engage in behaviors that become compulsive and often continue despite harmful consequences.
>
> Prevention efforts and treatment approaches for addiction are generally as successful as those for other chronic diseases.

The ASAM Task Force also recommended that definitions for medication-assisted recovery (MAR) and medication-assisted treatment (MAT), which had been previously identified as transitional terms, be retired from use in ASAM documents. With the evolution of addiction treatment and its increasing integration with general medical care, the Task Force recommended that ASAM adopt general medical terminology to describe addiction treatment [10].

EPIDEMIOLOGY OF CHRONIC PAIN AND OPIOID MISUSE

Chronic pain affects about 100 million American adults—more than the total affected by heart disease, cancer, and diabetes combined [2]. It also costs the nation up to $635 billion each year in medical treatment and lost productivity and is the leading reason for receiving disability insurance [3; 11]. The lifetime prevalence of chronic pain ranges from 54% to 80%, and among adults 21 years of age and older, 14% report pain lasting 3 to 12 months and 42% report pain that persists longer than one year [2]. While 5 to 8 million Americans receive long-term opioids for the management of chronic pain, an

estimated 41% of patients with chronic pain report their pain is uncontrolled, and 10% of all adults with pain suffer from severe, disabling chronic pain [11].

The increasing prevalence of chronic pain is the result of multiple factors, including the aging population; rising rates of obesity and obesity-related pain conditions, such as joint deterioration; advances in life-saving trauma interventions; poorly managed post-surgical pain; and greater public awareness of pain as a condition warranting medical attention [2]. In addition, many armed forces veterans have been returning from military action in Afghanistan and Iraq with traumatic injuries and chronic pain, and veterans' care clinicians have been reporting the perception that long-term pain management is lacking support in the veteran healthcare infrastructure [12].

There is a widespread misperception that opioid analgesic prescribing and overdose continues to grow, fueling an opioid epidemic [13; 14; 15; 16; 17]. Data from a 2019 Centers for Disease Control and Prevention (CDC) surveillance report show that between 2006 and 2018, the annual prescribing rate per 100 persons decreased from 72.4 to 51.4 for all opioids, an overall reduction of 29.0% [18]. (Opioid prescriptions, including codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, propoxyphene, tapentadol, tramadol, and buprenorphine, were identified using the National Drug Code. Cough and cold formulations containing opioids were not included.) The rate for all opioid prescriptions initially increased annually by 1.9% from 2006 to 2012, but then decreased annually by 5.2% from 2012 to 2016, and continued to decrease annually by 12.4% from 2016 to 2018 [18].

Although the epidemic of drug overdoses that began in the 1990s primarily involved prescription opioids prescribed for analgesia, the rapid increase in overdose deaths in 2010 was primarily attributed to heroin, and in 2013, to synthetic opioids, particularly illicitly manufactured fentanyl [18]. A total of 70,237 drug overdose deaths occurred in 2017, a rate of 21.7 per 100,000 persons. Although deaths might have involved more than one drug, prescription and/or illicit opioids were involved in 67.8% (47,600) of these drug overdose fatalities. Among opioid-involved deaths, the category synthetic opioids other than methadone (primarily illicitly manufactured fentanyl) was the most common, with 28,466 deaths. The prescription opioids category, which includes natural and semisynthetic opioids (e.g., oxycodone, hydrocodone) and methadone, was the second most common, with 17,029 deaths. Heroin was involved in 15,482 deaths. Natural and semi-synthetic opioids were involved in 14,495 deaths, and methadone was involved in 3,194 deaths. Cocaine was involved in 13,942 deaths, and 10,333 persons died from drug overdoses involving psychostimulants with abuse potential (e.g., methamphetamine) [18].

There is nearly universal agreement that opioid analgesics were injudiciously overprescribed during the 2000s. Interpretation of the broader trend of increased prescribing from 1990 might be viewed by public health professionals as entirely problematic and by pain medicine professionals as necessary in part, given the past neglect of patients in pain. This reflects the polarized nature of pain care and opioid analgesic prescribing in particular. Efforts to reduce opioid analgesic overprescribing and associated overdose have been successful but have come at a cost to patients who have faced increasing barriers to access, including stigma and abuse in a healthcare system, tapering of opioids without consideration for pain or functional improvements, and difficulty finding a physician [14; 19; 20].

Worldwide consumption of opioid analgesics increased dramatically over the past few decades, driven primarily by U.S. consumption. For example, the global consumption of oxycodone was 3 tons (2,722 kg) in 1990 and 77 tons (69,853 kg) in 2009, with 62 tons (81%) consumed in the United States [21]. Despite a decrease in global manufacture of the drug, global consumption of oxycodone increased, from 51.6 tons in 2019 to 64.9.6 tons in 2020. Consumption remained concentrated in the United States, which consumed 44.3 tons (68.2%) of the world total [22]. Global stocks of oxycodone decreased to 85.9 tons in 2020, with the United States holding 38.3 tons, or 44.7% of the world's total [22]. The United States also accounted for almost all (99.2%) of the global manufacture of hydrocodone [22]. This is partially because access to opioid analgesics is virtually or entirely non-existent for much of the world's population. An estimated 3.6 billion people (50% of the global population who reside in the poorest countries) receive less than 1% of the distributed opioids [23]. Other countries with adequate opioid access prefer dihydrocodeine or low-dose morphine over hydrocodone for use in moderate or moderately severe pain [24].

Many prescribed opioid analgesic fatalities result from the co-ingestion of central nervous system (CNS)/respiratory depressants (especially benzodiazepines) or prescribed methadone. The National Institute on Drug Abuse reported benzodiazepines contributed to 13.4% of opioid analgesic fatalities in 2020 (compared with 24% in 2017), but this may underestimate the true contribution [25]. A Canadian study evaluated 607,156 adults prescribed opioids for noncancer pain, and of those whose deaths were related to opioids, co-prescribed benzodiazepines were detected in 84.5% [26]. In another study of 2,182,374 North Carolina residents receiving one or more opioid analgesics in 2010, benzodiazepines were present in 61.4% who fatally overdosed [27]. A cross-sectional study of 386,457 ambulatory care visits in the United States from 2003 through 2015 found that the use of benzodiazepines increased substantially from 3.8% to 7.4% of visits, including co-prescribing with other sedating medications [28]. Use for back and chronic pain increased more significantly than use for anxiety and insomnia, which remained relatively unchanged. This increase likely reflects not only a growing number of individuals receiving benzodiazepines, but also an increase in those receiving them on a long-term basis, despite the lack of evidence supporting their use past 8 or 10 weeks [28].

OPIOID MISUSE IN FLORIDA

In Florida, misuse of prescription opioids became a serious problem in the 1990s and 2000s, but efforts to stem the problem appear to be working. The rate of drug overdose deaths increased 58.9% during 2003–2010, and in 2009, one in eight deaths in Florida was attributable to drug overdose [29; 30]. From 2019 to 2020, total drug-related deaths increased by 17%. Opioid-related deaths increased by 28%, and opioid-caused deaths increased by 42% [31].Of the 6,089 opioid-caused deaths reported in Florida in 2020, 1,187 of these deaths were attributed to oxycodone, a 5% increase in oxycodone-caused deaths over the previous year [31]. These trends resulted in the enactment of several measures to address prescribing that was inconsistent with best practices, and partnership with the U.S. Drug Enforcement Administration (DEA) to close and prevent "pill mills" from introducing millions of opioid dose units into illicit markets [32; 33]. In May 2017, former Florida Governor Rick Scott signed an executive order declaring the opioid epidemic a public health emergency, providing additional funding and empowering state health professions to take steps to address this pressing issue [33]. As part of this order, the State Health Officer has issued a standing order for opioid antagonists to ensure emergency responders have access [33]. The order has been extended several times (last in 2019) [34].

Drug overdose fatalities in Florida have continued rising from increased use of heroin, synthetic cannabinoids, and novel psychoactive substances such as alpha-PVP ("flakka"). An influx of clandestine fentanyl into Florida in early 2014, and several fentanyl analogs and other novel non-pharmaceutical opioids more recently, has largely driven the increases in opioid overdose fatalities [31]. Several overdose fatalities in Florida were linked to counterfeit alprazolam, oxycodone, and hydrocodone tablets that contained fentanyl [35]. The decrease in prescription opioid fatalities, offset by increasing overdose fatalities from other opioid and non-opioid agents, reflects the intervention focus on the supply side ("pill mill laws") and neglect of treatment funding that would address the demand side of problematic drug use [36].

In Florida, fatalities with benzodiazepines present peaked in 2010 with 6,188, falling to 4,405 in 2020 (37.7% were alprazolam) [31]. Of the 44,577 deaths investigated by Florida authorities, toxicology results determined that drugs were present at the time of death in 14,708 individuals, with the vast majority revealing more than one drug occurrence [31]. Other primary contributors to opioid analgesic-related fatalities include alcohol and prescribed methadone [31; 37; 38].

In addition to the executive order issued in 2017 (and subsequently extended), several new state laws were passed in 2018 to impose additional legal requirements on controlled substance prescribers [39]. These laws will be discussed in detail later in this course.

INITIATION AND MANAGEMENT OF THE PATIENT WITH PAIN

In 2016, the CDC issued updated opioid prescribing guidelines for chronic pain that address 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 [40]. Some of the recommendations are standard risk mitigation approaches, but others have been criticized by pain medicine physicians and patient advocates. A common criticism is the sole focus on curtailing prescribing and patient access [41; 42; 43; 44]. The 2016 guidelines communicated the intent to evaluate and reassess evidence and recommendations as new evidence became available. In 2022, the CDC posted a draft of updated guidelines for public comment, based on systematic reviews of new evidence [45; 46; 47]. Release of a final updated guideline is anticipated in late 2022 [45]. Meanwhile, the recommendations referred to in this course are taken from the CDC's 2016 opioid prescribing guideline [40].

It can be difficult to balance the benefits and harms of prescription opioids. This is exacerbated by inadequate education and by opioid prescribing guidelines based on expert opinion instead of scientific evidence. This has resulted in wide variation in clinical practice, inconsistent prescriber guidance, and clinician confusion [48]. For instance, the CDC and other opioid guidelines state that opioids should be considered only after non-opioid therapy fails. However, when pain is severe and patients require powerful analgesic control, there is little choice because no other pain medications are as effective as opioids with lower addiction risk [49].

However, many guidelines do share common recommendations. These represent the current "conventional wisdom" in opioid analgesic prescribing and can inform healthcare professionals of the best clinical practices in opioid prescribing that include approaches to the assessment of pain and function and pain management modalities. Pharmacologic and nonpharmacologic approaches should be used on the basis of current evidence or best clinical practice. Patients with moderate-to-severe chronic pain without adequate pain relief from non-opioid or nonpharmacologic therapy can be considered for a trial of opioid therapy [40; 50]. Initial treatment should always be considered individually determined and as a trial of therapy, not a definitive course of treatment [51].

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 [40].

RISK STRATIFICATION FOR PATIENTS PRESCRIBED OPIOIDS
Low Risk
No past or current personal history of alcohol/substance use disorder (AUD/SUD) No or minimal co-occurring psychiatric disorders No family history of alcoholism or substance abuse
Medium Risk
Past history of AUD or SUD Moderate concomitant psychiatric disorders Family history of alcoholism or substance abuse/addiction Patient history of physical, emotional or sexual abuse, especially in childhood
High Risk
Patient actively addicted to or abusing opioids, illicit drugs or alcohol Untreated or poorly controlled major psychiatric disorder History of diversion, prescription forgery, selling their prescription drugs
Source: [58; 59; 60] *Table 1*

Florida law dictates that, for the treatment of acute pain, a prescription for an opioid drug may not exceed a three-day supply; an exception may be made for a seven-day supply if [52]:

- The prescriber, in his or her professional judgment, believes that more than a three-day supply of such an opioid is medically necessary to treat the patient's pain as an acute medical condition.
- The prescriber indicates "ACUTE PAIN EXCEPTION" on the prescription. (For the treatment of pain other than acute pain, a practitioner must indicate "NON-ACUTE PAIN" on a prescription.)
- The prescriber adequately documents in the patient's medical records the acute medical condition and lack of alternative treatment options that justify deviation from the three-day supply limit.

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 [53; 54; 55].

As part of House Bill 21, passed in 2018, the Florida Board of Medicine and the Board of Osteopathic Medicine are required to establish guidelines for prescribing controlled substances for acute pain [52]. In 2019, the Florida Board of Medicine approved and published *Rule No. 64B8-9.013, Standards for the Prescribing of Controlled Substances for the Treatment of Acute Pain* to satisfy this requirement [56].

PATIENT EVALUATION 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***). 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 [40; 57].

Anxiety disorders, major depressive disorder, and intense emotional distress alter pain perception and response. Intensity and perception of reported pain is also influenced by factors such as mood, cultural background, social supports, and financial resources. A biopsychosocial model is required to inform pain assessment in order to address the biologic basis of pain and presence of social and psychologic contributors [49].

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

Depression is perhaps the single most important comorbidity in patients with chronic pain and is vastly underdiagnosed and untreated. Patients with unrecognized and untreated depression are unlikely to respond to opioids and other pain therapies, but successful treatment of depression can promote analgesia [61].

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 [40; 62].

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 tool use 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 [63].

EVIDENCE-BASED PRACTICE RECOMMENDATION

Despite limited evidence for reliability and accuracy, screening for opioid use is recommended by the American Society of Interventional Pain Physicians, as it will identify opioid abusers and reduce opioid abuse.

(https://painphysicianjournal.com/2012/july/2012;%2015;S67-S116.pdf. Last accessed August 16, 2022.)

Level of Evidence: Limited (Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality trials, important flaws in trial design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.)

Opioid Risk Tool (ORT)

The Opioid Risk Tool (ORT) is a five-item 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 [64; 65].

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 [66; 67].

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 [68; 69].

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

The Diagnosis, Intractability, Risk, and Efficacy (DIRE) risk assessment tool is a clinician-rated questionnaire that is used to predict patient compliance with long-term opioid therapy [70; 71]. Patients scoring lower on the DIRE tool are poor candidates for long-term opioid analgesia.

Mental Health Screening Tool

The Mental Health Screening Tool is a five-item screen that asks about a patient's feelings of happiness, calmness, peacefulness, nervousness, and depression in the past month [72]. A lower score on this tool is an indicator that the patient should be referred to a specialist for pain management.

CREATING A TREATMENT PLAN

Opioid therapy 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; 40]. The treatment plan should describe therapy selection, measures of progress, and other diagnostic evaluations, consultations, referrals, and therapies. All patients prescribed an opioid for pain related to a traumatic injury (severity score ≥9) should be concurrently prescribed an antagonist (e.g., naloxone) [52].

In opioid-naïve patients, start at the lowest possible dose and titrate to effect. Dosages for opioid-tolerant patients should always be individualized and titrated by efficacy and tolerability [1]. 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 be knowledgeable of federal and state opioid prescribing regulations. Issues of equianalgesic dosing, close patient monitoring during all dose changes, and incomplete cross-tolerance with opioid conversion should be considered.

If necessary, treatment may be augmented, with preference for non-opioid and immediate-release opioids over long-acting/extended-release opioids. Taper opioid dose when no longer needed [62].

Non-Opioid Pain Management Options

Nonpharmacologic Approaches

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.

Methods to provide distraction from pain come in a wide variety, including reciting poetry, meditating with a calm phrase, watching television or movies, playing cards, visiting with friends, or participating in crafts. Music therapy and art therapy are also becoming more widely used as nonpharmacologic options for pain management.

Non-Opioid Analgesics

Non-opioid analgesics, such as aspirin, acetaminophen (Tylenol), and nonsteroidal anti-inflammatory drugs (NSAIDs), are primarily used for mild pain and may also be helpful as coanalgesics for moderate and severe pain. Acetaminophen is among the safest of analgesic agents, but it has essentially no anti-inflammatory effect. Toxicity is a concern at high doses, and the maximum recommended dose is 3–4 g per day [73]. Acetaminophen should be avoided or given at lower doses in people with a history of alcohol abuse or renal or hepatic insufficiency [73].

NSAIDs are most effective for pain associated with inflammation. Among the commonly used NSAIDs are ibuprofen (Motrin, Advil), naproxen (Aleve, Naprosyn), and indomethacin (Indocin). There are several classes of NSAIDs, and the response differs among patients; trials of drugs for an individual patient may be necessary to determine which drug is most effective [74]. NSAIDs inhibit platelet aggregation, increasing the risk of bleeding, and also can damage the mucosal lining of the stomach, leading to gastrointestinal bleeding. There is a ceiling effect to the non-opioid analgesics; that is, there is a dose beyond which there is no further analgesic effect. In addition, many side effects of non-opioids can be severe and may limit their use or dosing.

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 [1].

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" [75]:

- 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 [76]:

- 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 concerning adverse effects and risks of overdose or diversion [1]. Satisfactory therapy is indicated by improvements in pain, function, and quality of life. It is important to remember that for some patients with severe chronic pain, improved function may take longer than pain control. Either pain or function (not both) will improve. In some cases, preventing worsening pain/

functional impairment is the best achievable outcome. 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 or the partner of the patient can provide the clinician with valuable information that better informs decision making regarding continuing opioid therapy [1]. 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 [1]. 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 [76]:

- 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 [77; 78].

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 with 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 [57]. 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 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 for patients with chronic pain who are receiving opioid therapy, and the Pain Assessment and Documentation Tool (PADT) was designed to address these shortcomings [79]. 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 [80]. 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 [72].

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***) [81]. The CDC 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 [40]. However, this recommendation was based on low-quality evidence that indicates little confidence in the effect estimate.

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	3 times per year	4 times per year

Source: [81] *Table 2*

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.

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 [82].

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 FDA has developed a patient counseling document 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 [62]. A copy of this form may be accessed online at https://www.fda.gov/media/79776/download.

When prescribing opioids, clinicians should provide patients with the following information [62]:

- 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 [83]. According to the Office of National Drug Control Policy, 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 [84]. 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 [85]. Patients should be advised to flush prescription drugs down the toilet only if the label or accompanying patient information specifically instructs doing so and no other disposal method is appropriate [85].

The American College of Preventive Medicine has established best practices to avoid diversion of unused drugs and educate patients regarding drug disposal [83]:

- 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; 40].

Clinicians should provide physically dependent patients 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 [82]. Cannabis use for chronic pain in patients receiving opioid therapy continues to receive increased interest and support; however, experts caution that more evidence of improved patient outcomes is needed [86; 87; 88].

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.

CRISIS INTERVENTION: MANAGEMENT OF OVERDOSE

Individuals who have first contact with persons suspected of experiencing an opioid-related overdose are in the position to intervene to prevent the potentially devastating consequences. In these cases, care begins with crisis intervention directed at immediate survival by reversing the potentially lethal effects of overdose with an opioid antagonist.

Opioid antagonists have obvious therapeutic value in the treatment of opioid overdose. A 2012 study found that wider distribution of naloxone and training in its administration might have prevented numerous deaths from opioid overdoses in the United States [89]. Since the first community-based opioid overdose prevention program began distributing naloxone in 1996, more than 10,000 overdoses have been reversed [89].

In Florida, licensed healthcare providers may prescribe and pharmacists may dispense opioid antagonists (even as a standing order) for at-risk individuals, these individuals' relatives or other caregivers, and emergency responders to be used in their course of duties [90]. Emergency responders include (but are not limited to) law enforcement officers, paramedics, and emergency medical technicians [90]. As noted, there is a statewide standing order for naloxone for all emergency responders in Florida [33].

OPIOID ANTAGONISTS

Relatively minor changes in the structure of an opioid can convert an agonist drug into one with antagonistic actions at one or more opioid receptor types. Opioid antagonists include naloxone, naltrexone, and nalmefene. Interestingly, naloxone also appears to block the analgesic effects of placebo medications and acupuncture. These agents have no abuse potential [91].

In response to acute overdose, the short-acting opioid antagonist naloxone is considered the gold standard, and it remains the most widely used opioid antagonist for the reversal of overdose and opioid-related respiratory depression. It acts by competing with opioids at receptor sites in the brain stem, reversing desensitization to carbon dioxide, and reversing or preventing respiratory failure and coma. There is no evidence that subcutaneous or intramuscular use is inferior to intravenous naloxone. This has prompted some states to pass laws allowing opioid antagonists to be available to the general public for administration outside the healthcare setting to treat acute opioid overdose [92].

When used for opioid overdose, a dose of 0.4–2 mg of naloxone is administered intravenously, intramuscularly, or subcutaneously [93]. If necessary, the dose may be repeated every two to three minutes for full reversal. For ease of use, naloxone is also available in a pre-filled auto-injection device. An intranasal formulation is also available in doses of 2 mg, 4 mg, or 8 mg [93]. It is important that standard Advanced Cardiac Life Support (ACLS) protocols be continued while naloxone is being administered and that medical treatment (at a healthcare facility) be given immediately.

COMPLIANCE WITH STATE AND FEDERAL LAWS

In response to the rising incidence in prescription opioid abuse, addiction, diversion, and overdose in the late 1990s and 2000s, the FDA has mandated opioid-specific REMS to reduce the potential negative patient and societal effects of prescribed opioids. 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 [76].

Several regulations and programs at the state level have been enacted in an effort to reduce prescription opioid abuse, diversion, and overdose, including [94]:

- 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 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.

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 [95]. 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.

In Florida, the prescribing, dispensing, and consumption of certain controlled substances are governed by Chapter 893 of the Florida Statutes [96]. This law establishes the standards for controlled substance prescribing, including reporting system requirements, for prescribers and pharmacists in Florida. As of 2022, the Florida schedule of controlled substances aligns with the DEA schedule [97].

THE ELECTRONIC FLORIDA ONLINE REPORTING OF CONTROLLED SUBSTANCES EVALUATION PROGRAM

Emerging trends and patterns of prescription opioid abuse, addiction, and overdose are monitored by several industry and government agencies through data collection from a variety of sources. These include health insurance claims; the Automation of Reports and Consolidated Orders System, a DEA-run program that monitors the flow of controlled substances from manufacturing through distribution to retail sale or dispensing; the Treatment Episode Data Set, which monitors treatment admissions; the National Center for Health Statistics state mortality data; and the Researched Abuse, Diversion, and Addiction-Related Surveillance System, which monitors prescription drug abuse, misuse, and diversion [98; 99; 100; 101].

Almost all states, including Florida, have enacted PDMPs to facilitate the collection, analysis, and reporting of information on controlled substances prescribing and dispensing [1]. All prescribers must consult the Electronic Florida Online Reporting of Controlled Substances Evaluation (E-FORCSE) to review a patient's controlled substance dispensing history before prescribing or dispensing a controlled substance to a patient 16 years of age or older [39; 102]. This is mandated even for existing patients and should be done each time a controlled substance is prescribed or dispensed [39]. If the system is nonoperational or cannot be accessed due to a temporary technologic or electrical failure, the prescription may be issued (with documentation of the exception) for up to a maximum three-day supply.

All clinicians who prescribe or dispense controlled substances are required to report the action to E-FORCSE as soon as possible, but no later than the close of the next business day [39]. This should be repeated each time the substance is dispensed. This reporting requirement is waived in certain circumstances, including for [103]:

- The dispensing of a controlled substance in the healthcare system of the Department of Corrections
- The dispensing of a controlled substance to a person younger than 16 years of age

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 patient with pain). This information carries with it substantial public policy and regulatory implications. The 2020 National Survey on Drug Use and Health asked 9.3 million non-medical users of prescription opioids how they obtained their most recently used drugs [104]. Among persons 12 years of age or older, 47.2% obtained their prescription opioids from a friend or relative. Of this, 34.4% got the prescription opioids from a friend or relative for free, 9.2% bought them from a friend or relative, and 3.7% took them from a friend or relative without asking. Another 42.0% got their opioids through a prescription from one doctor (vs. 35.4% in 2016) [104]. Less frequent sources included a drug dealer or other stranger (6.2%); multiple doctors (1.0%); theft from a doctor's office, clinic, hospital, or pharmacy (0.6%) (vs. 0.7% in 2016); and some other way (3.1%) [104].

As discussed, UDTs can give insight into patients who are misusing opioids. A random sample of UDT results from 800 patients with pain treated 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 [105]. 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 [106].

In addition to aberrant urine screens, there are certain behaviors that are suggestive of an emerging opioid use disorder. The most suggestive behaviors are [82; 107; 108]:

- 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 less association with opioid misuse include [82; 107; 108]:

- 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 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, the most 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" [83]. In addition, patients should be aware of the many options available to treat chronic pain aside from opioids. As stated, 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 [83]. It is also best practice to periodically request a report from the E-FORCSE to evaluate the prescribing of opioids to your patients by other providers [39; 83].

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 [83; 109]. 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 [109].

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' fiduciary responsibility to patients entails an obligation to support continuity of care for their patients" [110]. While physicians have the option of withdrawing from a case, they cannot do so without giving notice to the patient, the relatives, or responsible friends sufficiently long in advance of withdrawal to permit another medical attendant to be secured or to facilitate the transfer of care, when appropriate [110]. The notice of termination should be sent in writing, should specifically note the cause(s) for the termination, and should give a period of time prior to termination, usually 30 days [111]. 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 [112].

CASE STUDY

An unemployed man, 64 years of age, is brought to an emergency department by ambulance, after his wife returned from work to find him lying on the couch, difficult to arouse and incoherent. He has a past history of hypertension, diabetes (non-insulin dependent), mild chronic obstructive pulmonary disease, and chronic back and shoulder pain, for which he has been prescribed hydrocodone/acetaminophen for many years. His wife reports that while he seemed his usual self when she left for work that morning, he had, in recent weeks, been more withdrawn socially, less active, and complained of greater discomfort from the back and shoulder pain. She knows little about his actual medication usage and expresses concern that he may have been taking more than the prescribed amount of "pain medicine."

On evaluation, the patient is somnolent and arouses to stimulation but is non-communicative and unable to follow commands. His blood pressure is normal, he is afebrile, and there are no focal neurologic deficits. Oxygen saturation, serum glucose, and routine laboratory studies (blood counts and metabolic profile) are normal except for mild elevation in blood urea nitrogen (BUN) and creatinine; the urine drug screen is negative except for opioids. Additional history from the family indicates that the patient has been admitted to other hospitals twice in the past three years with a similar presentation and recovered rapidly each time "without anything being found."

Following admission, the patient remains stable-to-improved over the next 12 to 18 hours. By the following day, he is awake and conversant and looks comfortable. On direct questioning, he reports recent symptoms of depression but no suicidal ideation. The patient describes an increased preoccupation with his pain syndrome, difficulty sleeping at night, and little physical activity during the day, in part because of physical discomfort. He is vague about his medication regimen and admits to taking "occasional" extra doses of hydrocodone for pain relief.

The family is instructed to bring in all his pill bottles from home, which they do. In addition to the hydrocodone prescribed by his primary care physician, there is a recent refill of a prescription for the medication given to the patient at the time of his last hospital discharge six months earlier.

ASSESSMENT

A full evaluation, including radiographic studies and consultation with psychiatry and physical therapy, is completed. The working diagnosis for the patient's acute illness is toxic encephalopathy caused by the sedative side effects of opioid medication on the CNS. It is explained that the combination of his advancing age and diabetes likely reduced the efficiency of his kidneys in clearing the medication and its metabolites, making him more susceptible to CNS sedation. It is noted that the patient and his wife have little understanding of the rationale, proper use and safeguards, potential side effects, and limited effectiveness of opioid use for chronic pain.

In addition, the patient is diagnosed with poorly controlled chronic pain syndrome secondary to osteoarthritis and degenerative disc disease; exacerbating factors include deconditioning and reactive depression. The use of an opioid analgesic, at least for the near term, is considered appropriate, if dosed properly, monitored closely, and integrated into a comprehensive, multidisciplinary plan that includes treatment of depression and the use of adjunctive, nonpharmacologic modalities of care. In the setting of possible early diabetic nephropathy, the option of utilizing an NSAID, except for very brief periods of break-through pain, is not considered to be a safe option.

At discharge, and in consultation with his primary care physician, a written treatment and management plan addressing all aspects of the patient's care is presented to the patient and his wife for discussion and consent. Among the key issues addressed are:

- Goals: Improvement in subjective pain experience; improved function of daily living manifested by regular walking exercise and improved social interaction with family and friends; relief of depression; and in the long-term, anticipated withdrawal of opioid medication and resumption of part-time work and/or volunteer community activity
- Outpatient physical therapy and back exercise program to increase core muscular strength, improve flexibility, reduce pain, and increase exercise tolerance
- Patient and family counseling regarding the safe use, dosage regulation, side effects, and proper disposal of opioid medication
- Joint patient-physician responsibilities as regards to regular follow-up, monitoring of goals and treatment effectiveness, avoidance of "doctor-shopping," and assent to single provider for prescription medication

FOLLOW-UP

On follow-up six weeks after discharge, the patient is noticeably improved. He reports that he feels stronger and is sleeping better. His affect is brighter, and he is getting out more. He has maintained his physical therapy and exercise routine and is compliant with his medication. Though he still has pain, it is noticeably less and he is coping better. He and his wife are encouraged by his progress, particularly in regard to his improved functional status.

CONCLUSION

For patients suffering from pain, prescribed opioid analgesics may substantially lessen pain, distress, and impairment. Inappropriate overprescribing and overdose related to opioid analgesics increased dramatically in the 2000s. These trends are in multi-year reversal, but patient safety and risk mitigation remains no less important, and clinical tools, guidelines, and recommendations are available for use when prescribing opioids to patients with pain. 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 64–65.

COURSE TEST
#91152 STRATEGIES FOR APPROPRIATE OPIOID PRESCRIBING: THE FLORIDA APRN/PA REQUIREMENT

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 August 31, 2025.

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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. Data indicate that opioid analgesic prescribing and overdose peaked in
- A) *2010.*
- B) *2001.*
- C) *1990.*
- D) *1981.*

3. In the absence of other risk factors, a patient prescribed opioids for chronic pain who has no personal or family history of alcohol or substance abuse 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 five 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) *three to six months.*
- C) *6 to 12 months.*
- D) *one to two years.*

7. According to the Office of National Drug Control Policy, most unnecessary or expired medications should be disposed of
- A) *in their original container.*
- B) *by flushing down the toilet.*
- C) *after being mixed with undesirable substances.*
- D) *by offering or selling to others who need the medication.*

8. 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*

9. All clinicians who prescribe or dispense controlled substances are required to report the action to the Electronic Florida Online Reporting of Controlled Substances Evaluation (E-FORCSE) within

A) two hours.
B) one business day.
C) 30 days.
D) six months.

10. 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

Be sure to transfer your answers to the Answer Sheet insert located between pages 64–65.
PLEASE NOTE: Your postmark or facsimile date will be used as your test completion date.

Chronic Cough in Adults

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.

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John M. Leonard, MD

Senior Director of Development and Academic Affairs
Sarah Campbell

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

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INTRODUCTION

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

BACKGROUND

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.

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.

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*

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].

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].

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*

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.

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

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

Level of Evidence: Expert Opinion/Consensus Statement

INITIAL EVALUATION OF CHRONIC COUGH

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

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

DEFINITIONS OF COUGH

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

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

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

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

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

PATIENT HISTORY

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

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

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

PHYSICAL EXAMINATION

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

MANDATORY INITIAL TESTS

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

EVIDENCE-BASED PRACTICE RECOMMENDATION

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

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

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

"RED FLAG" ASSESSMENT OF SERIOUS UNDERLYING CAUSES OF COUGH

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

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

RECORDS REVIEW

If patients have undergone prior evaluations for upper airway cough syndrome, asthma, GERD, or nonasthmatic eosinophilic bronchitis, obtain and review these medical records, including laboratory values, diagnostic reports, and treatments prescribed, to determine if these etiologies have been accurately assessed, diagnosed, and treated. Patients may not have been completely evaluated for these conditions yet diagnosed based on their response (or lack thereof) to empiric trials, which is important to ascertain [2].

THE ANATOMIC DIAGNOSTIC PROTOCOL (ADP)

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

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

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

DIAGNOSTIC TESTS

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

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

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].

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*

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 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

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*

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

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

THE "TREATABLE TRAITS" APPROACH IN CHRONIC AIRWAY DISEASES

In the 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.

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

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

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

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

EMPIRIC TREATMENT APPROACH

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

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

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

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

When the cause of chronic cough is identified or suspected, there are two options [26; 44; 57; 109]. The first is to pursue one diagnostic and treatment path at a time; with incomplete response of the cough to one line of therapy, adding therapy for the next most likely diagnosis is reasonable. The second option in patients with more than one suspected cause and

a cough that is especially disruptive is to empirically treat or evaluate the likely causes simultaneously. After the cough resolves, treatments can be stopped sequentially, starting with the least likely to have been helpful, observing the patient for any return of cough.

BEHAVIORAL TREATABLE TRAITS

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

Smoking cessation improves cough by resolving chronic bronchitis. Nicotine suppresses the cough reflex, and nicotine withdrawal due to smoking cessation may 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].

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,

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*

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
- 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

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*

assumption that the diagnosis (e.g., asthma, COPD) is well-established and clear, a situation that is not the case in many instances in clinical practice, particularly in primary care. This is a fundamental, but often overlooked, issue in the current guideline-directed management of airway diseases [14; 16].

Pulmonary and Extrapulmonary Traits as "Connected Comorbidities"

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

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

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

The Argument for Thoroughness

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

PITFALLS IN THE MANAGEMENT OF CHRONIC COUGH
Upper Airway Cough Syndrome
Failing to recognize that upper airway cough syndrome (also asthma or GERD) can present as a cough-phlegm syndrome, misdiagnosed as chronic bronchitis. Assuming that all histamine H1 receptor antagonists (H1RAs) are the same. H1RAs without anticholinergic activity do not help nonallergic rhinitis conditions. Further, anticholinergic H1RAs may adversely affect memory, glaucoma, and prostate problems. Instead, consider ipratropium bromide nasal therapy. Failing to consider: • "Silent" upper airway cough syndrome when a patient does not sense a postnasal drip or realize their frequent throat clearing • Allergic rhinitis and recommend the avoidance of allergens because symptoms are perennial • Sinusitis because it is nonobvious • NSAID-exacerbated disease • The potentially beneficial role of upper respiratory endoscopy
Asthma
Failing to recognize that: • Asthma can present as cough alone (i.e., cough-variant asthma) • Inhaled medications may exacerbate cough • Positive methacholine challenge alone is not diagnostic of asthma
Nonasthmatic Eosinophilic Bronchitis
Failing to consider the diagnosis, occupational/environmental causes, or order the correct test
GERD
Failing to recognize that: • "Silent" reflux disease can be causal and that it may take two to three months of intensive treatment before cough starts to improve and five to six months to resolve • GERD can be worsened by comorbidities (e.g., obstructive sleep apnea) or their treatment (e.g., nitrates or calcium channel blockers for coronary artery disease, progesterone for hormone replacement) Assuming that: • Cough cannot be due to GERD because cough remains unchanged when gastrointestinal symptoms improve • Vocal cords' appearance can diagnose GERD, when inflammatory changes from coughing can mimic those of reflux Being unaware that acid suppression alone will not improve cough Failing to consider: • Non-acid reflux disease • The role of diet, intense exercise, and prokinetic therapy • Adequately treat co-existing causes of cough that perpetuate the cycle of cough and reflux because cough can provoke reflux
Triad of Upper Airway Cough Syndrome, Asthma, and GERD
Failing to consider that more than one condition may be contributing simultaneously to cough, or failing to consider additional contributing conditions because of another "obvious" cause (e.g., COPD) Failing to appreciate: • These chronic disorders cannot be cured and will periodically flare, especially with viral illness • When cough flares after a period of remission, re-evaluate as if a new problem • Asthma may become a problem when it was not before
Unsuspected Airway Diseases
Failing to perform bronchoscopy when chest x-ray and CT are normal. Transnasal route allows inspection of both upper and lower respiratory tracts. Failing to appreciate that prolonged IV therapy for suppurative airway disease may succeed when the same drug given orally failed
Source: [6; 80] *Table 7*

In a 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].

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 diz-

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*

ziness (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].

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

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

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

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

In another study, twice daily pregabalin 75 mg was prescribed to 50 consecutive patients with refractory or unexplained chronic cough for three months. Pregabalin response, defined as LCQ total score improvement of ≥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, multicenter 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 European Respiratory Society suggests a trial of cough control therapy (physiotherapy/speech and language therapy) in adult patients with chronic cough.

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

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

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

Education

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

Vocal Hygiene

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

Cough Control/Suppression Training

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

Psychoeducational Counseling

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

Local Injection Therapies

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

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 64–65.

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.*

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 64–65.

PLEASE NOTE: Your postmark or facsimile date will be used as your test completion date.

Multiple Sclerosis

Audience
This course is designed for physicians, physician assistants, primary care providers, and nurses who may intervene to improve the lives of patients with multiple sclerosis.

Course Objective
This course provides physicians, nurses, and other healthcare providers with a review of the pathogenesis, clinical expression, diagnosis, and management of multiple sclerosis. Clinical care topics include treatment of acute exacerbations, therapeutic options for disease modification, and management of common symptoms and complications. The purpose of this course is to address knowledge gaps, enhance clinical skills, and improve quality of care and treatment outcomes for patients with multiple sclerosis.

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

1. Describe the risk factors for multiple sclerosis (MS).
2. Define the etiology and pathophysiology of MS.
3. Identify common signs and symptoms of MS.
4. Distinguish between the various MS disease courses, including relapsing-remitting, primary progressive, and secondary progressive subtypes.
5. Compare and contrast early-onset and late-onset MS.
6. Apply diagnostic criteria and select appropriate tests used to confirm the diagnosis of MS.
7. Assess the conditions that should be considered in the differential diagnosis of MS.
8. Select an appropriate treatment regimen for acute exacerbations of MS.
9. Discuss the role of disease-modifying therapy in the management of MS, including the expected benefit, mode of action, and selection of options available.
10. Anticipate and manage the various symptoms common to patients with active MS.
11. Devise a management plan for the patient with MS who is, or wishes to become, pregnant.

Faculty
John M. Leonard, MD, Professor of Medicine Emeritus, Vanderbilt University School of Medicine, completed his post-graduate 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, John M. Leonard, MD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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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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INTRODUCTION

Multiple sclerosis (MS) is an acquired, life-long disease of the central nervous system (CNS) that usually begins in early adulthood. In most cases, the early phase of disease is marked by clinical exacerbations and remissions, followed eventually by the gradual onset of fixed neurologic deficits. The cause of MS is unknown. The pathogenesis appears to involve the interplay of genetic predisposition, environmental exposures, and immune-mediated inflammatory demyelination within focal areas of the brain and spinal cord. With chronicity, the disease results in fixed damage to myelin, axons, and oligodendrocytes, leading to cumulative disability and impaired quality of life. The propensity for repeated episodic flares (clinical exacerbations) and multiple foci of tissue injury within the CNS, followed by healing with scar tissue (sclerosis), is what gives the disease its name. There is great variability in the clinical expression, neuroradiographic features, pathologic findings, and response to therapy.

At onset of illness, the clinical presentation reflects the focal nature of the neuroinflammatory process. Common presentations include acute unilateral vision loss (optic neuritis), diplopia (brain stem involvement), ataxia and nystagmus (cerebellum), and asymmetric limb weakness or sensory symptoms (partial myelopathy) [1; 2]. In the early stage of disease, the dominant pathologic finding is a well-demarked, focal lymphocytic inflammatory process within white matter (the plaque) causing demyelination and axonal injury [1; 3]. Initially, the inflammatory reaction subsides, healing and remyelination

take place to some degree, and clinical symptoms and signs remit. Over time, new lesions usually develop and clinical exacerbations of disease recur. In later stages, usually after 10 to 20 years, there is evidence of neuronal injury and multiple areas of degenerative change with some degree of brain atrophy. Treatment is based on the emerging body of evidence that MS is an autoimmune disorder characterized by activated T-cell, cytokine-mediated inflammation directed against components of axonal myelin. ß-interferon, monoclonal antibody, and other agents that modify certain sequences of the immune reaction have been utilized in the effort to modify the natural history of the disease and limit neurologic deficits. The response to these targeted therapies is variable; while they do reduce the frequency and expression of new episodes, the impact on disease progression and long-term neurologic disability is unclear.

Although some patients with MS experience a relatively benign course, most will eventually show signs of progressive neurologic deterioration, such as difficulty with ambulation and impaired cognition, that ultimately impact quality of life and impose a significant financial burden. In general, MS has minimal impact on life expectancy.

EPIDEMIOLOGY

MS is the most common immune-mediated (inflammatory) demyelinating disorder of the CNS. Most cases are diagnosed in persons between 15 and 50 years of age, and MS is a common cause of permanent disability in this segment of the population. MS in childhood and adolescence is being diagnosed more frequently, due in part to increased awareness and improved diagnostic imaging. Estimates are that 7,000 to 10,000 children and teenagers in the United States have MS [4; 5].

The lifetime incidence of MS in the general population is estimated to be 0.1%. The cumulative prevalence of MS in the United States is typically considered to be about 400,000, or 135 cases per 100,000 [1; 4; 6]. A 2019 study, using a method that employs a validated algorithm and healthcare datasets totaling 125 million adults, estimates the current prevalence of MS in the United States at close to 1 million individuals [4; 7]. Globally, approximately 2.5 million persons suffer from this disease. In general, MS is more prevalent in industrialized nations and in countries north of the equator.

The risk of developing MS is higher among women than men, with more than three times more women than men having the disease [4]. This is a trend that appears to have increased steadily in recent decades. A systematic review of incidence studies published between 1966 and 2007 found an incidence rate of 3.6 cases per 100,000 person-years in women, compared to 2.0 in men. The female-to-male ratio in MS incidence increased over time, from 1.4:1 in 1955, to 2.3:1 in 2000 [8]. Because MS follows a chronic course, this differential incidence leads to an even greater gender gap in prevalence of the disease.

The reason for female preponderance in MS is unknown and is the subject of intense scientific interest. The explanation may reside in the complex interplay of environmental, behavioral, and biologic factors, such as increasing exposure to environmental triggers associated with urbanization; decreasing number of pregnancies (a protective factor against relapses in MS); declining levels of vitamin D related to reduced sunlight exposure (affecting vitamin D-linked modulation of immune-mediated inflammation); and biologic differences in certain aspects of the immune system that are under the influence of sex hormones [9].

PREDISPOSING FACTORS

GENETICS

Genetic studies have demonstrated an inherited predisposition to acquiring MS, and epidemiologic investigations have identified several environmental factors that appear to increase the risk of developing MS [10; 11; 12]. Among first-degree relatives of an index case, the lifetime risk is 3% to 5%; for a monozygotic twin, the risk is 31% [4]. The identification of specific risk alleles, and the expression of their related gene products, is the subject of much interest and ongoing investigation [10; 11; 13; 14]. The largest and first identified genetic risk factor is an allele known as HLA-DRB1*15:01, which increases the risk of MS about threefold [15]. More than 200 genetic risk variants have now been described. Although single genetic effects are small in MS, they point to processes and cell subsets necessary for MS pathogenesis [15].

ENVIRONMENTAL FACTORS

Environmental factors are thought to play a significant role in the development of MS. Studies have shown an association between geographic latitude and risk, with the risk increasing from south to north [16; 17]. The lowest risk in found among persons living near the equator. As such, the prevalence of MS is higher in geographic locales having less sunlight exposure (and hence diminished production of vitamin D), suggesting that low levels of vitamin D may be a risk factor [17; 18; 19; 20]. In addition, persons who smoke have an increased relative risk compared to those who do not [17; 19; 21].

Certain infections acquired at a young age, and characterized by chronic latency and CNS trophism, have been implicated as risk factors [22]. These include mumps, rubella, Epstein-Barr virus, human herpesvirus 6, and *Chlamydia pneumoniae* [17; 23; 24; 25]. Patients with MS are more likely to have detectable levels of *C. pneumoniae* DNA in the cerebrospinal fluid (CSF) than patients with other neurologic diseases [17; 23]. The possibility that infection with one or more of these agents may be the principle cause, or trigger, for MS has also been investigated [17]. Genetic material and proteins specific to microbial agents have been identified in MS brain lesions, and specific T-cell or antibody responses in blood and CSF have been found in some patients with MS. However, the significance of these findings is uncertain.

There is considerable evidence that Epstein-Barr virus (EBV) infection acquired after childhood is a strong risk factor for MS [19]. EBV is a herpes-type virus most often acquired early in life; the prevalence of EBV seropositivity increases from about 50% in early childhood to greater than 90% by 30 years of age. Among young adults who are EBV seronegative, the risk of developing MS is 10 times lower than that of persons of the same age who are EBV-positive. Further, if primary EBV infection results in clinical infectious mononucleosis, the risk of MS increases two- to three-fold greater than the risk observed among EBV-seropositive persons without a history of infectious mononucleosis [19]. The temporal association between EBV infection and onset of MS was examined in a military study of EBV-seronegative service personnel, among whom the rate of EBV seroconversion (denoting primary infection) occurred at the rate of 11% per year [26]. Ten cases of MS were documented during the study period, and in all cases, the first symptoms of MS developed in the early years following EBV seroconversion (average interval: 3.8 to 5.6 years).

The role of viral infection and autoimmunity in the pathogenesis of MS has intrigued investigators and is the subject of a 2013 review [27]. One proposed mechanism is that direct infection of the brain causes inflammation and injury to myelin-producing cells, following which T-cells within the inflammatory milieu become sensitized to exposed epitopes on myelin fragments. These autoreactive T-cells then induce a series of cytokine-mediated inflammatory events that lead to further myelin destruction. Another possible mechanism is that simple persistence of a viral infection within the CNS leads to chronic inflammation and demyelination as the host immune response attempts to eliminate the infectious agent from the brain. An alternate mechanism, for which there is growing experimental evidence, involves the complex interplay of multiple viral infections and the host immune response, whereby systemic infection (outside the CNS) leads to activation of peripheral T-cells that are able to recognize "self" (myelin) as well as the inciting virus. Thus, the immune response to the virus acquires the capacity to cross-react with self (CNS myelin). In the setting of acute infection, these activated T-cells traverse the blood brain barrier and incite focal, immune-mediated inflammatory demyelination and MS [27].

It may be postulated that susceptibility to MS is conditioned by genetic predisposition combined with one or more acquired risk factors that impact immune surveillance and integrity of the blood-brain barrier. As stated, environmental risk factors include geographic latitude (e.g., sun exposure, vitamin D deficiency) and infection (e.g., latent CNS sequelae of childhood infection, EBV infection in young adulthood). Behavioral risk factors (e.g., cigarette smoking, obesity) have also been associated with increased risk of MS [19]. A population-based, case-control study in Sweden found that adolescent obesity conferred a 90% increased risk of developing MS in subsequent years [28]

PATHOGENESIS

Conceptually, MS is now considered to be an autoimmune inflammatory disorder with complex and variable pathologic features [1; 29]. Susceptible individuals are those of genetic predisposition in combination with environmental factors and possibly latent infection. The etiology is unclear, but initiation of disease appears to involve the activation of peripheral T-lymphocytes, programmed to recognize components of the CNS axonal myelin sheath. The disease is triggered by events that permit these autoactivated T-cells to breach the blood-brain barrier and cross-react with myelin components within the white matter of the brain and spinal cord [30]. This precipitates a cascade of immune-mediated inflammatory tissue injury. As seen on radiographic imaging and pathologic examination, the hallmark of the disease is this well-defined, focal zone of injury ("plaque") containing elements of inflammation, demyelination, and axon degeneration [1; 6]. Such lesions may be single or multiple, and over time, they may be partially reparative, relapsing, or recurrent in new locations. The location of lesions is variable; early in the disease they appear in white matter, often clustering near the ventricles and sparing peripheral nerves [14].

The autoimmune hypothesis of pathogenesis is supported in part by the following observations [29; 31]:

- Myelin antigen-specific, autoreactive T-cells have been isolated from peripheral blood lymphocytes.
- Immunologic studies in patients with MS have shown that relapses are preceded by expansion and activation of CD4+ T-cells in the peripheral immune compartment having myelin basic protein specificity.
- The histopathology of the MS plaque often shows a T-cell mediated (Th1-type) pattern of inflammation with interleukin-2 (IL-2) and chemokine expression.
- There is a linkage between these immunologic abnormalities and the activity of disease, as measured by clinical and magnetic resonance imaging (MRI) features.
- Experimental autoimmune encephalomyelitis, with histopathologic features of inflammation and demyelination similar to that seen in MS, can be induced in an animal model by immunization with myelin autoantigen.

The pathologic examination of active lesions reveals considerable heterogeneity with respect to structural change and immunologic features, indicating that multiple pathogenetic mechanisms may be involved in the disease process. In one carefully conducted study, the pattern of demyelination was analyzed in a series of active lesions from patients with MS [32]. The lesions could be grouped into four distinct patterns: two showed similarities to T-cell mediated or T-cell plus antibody-mediated autoimmune encephalomyelitis, and two showed a

ROLE OF INNATE IMMUNITY IN MS	
Innate Immune System Component	**Impact on Pathogenesis of MS**
Monocyte/macrophages	Hematopoietic monocytes and macrophages are the most abundant phagocytic cells of the innate immune system that infiltrate the MS lesion. Their morphology is very heterogeneous depending on which area of the MS lesion they have infiltrated. Monocytes/macrophages can contribute to neuroinflammation as well as promote neuroprotection in MS.
Microglial cells	Microglia provides the first-line of defense within the CNS. Microglial cells are phagocytic and clear debris resulting from inflammation. Upon activation, they can produce several proinflammatory cytokines (such as TNF) and reactive oxygen species that are toxic to infectious agents. They may also serve as antigen-presenting cells that directly activate T-cells.
Dendritic cells	Dendritic cells are potent antigen presenting cells and are considered to be the critical link that bridges the innate and adaptive immune responses. Because the CNS lacks conventional lymphatic circuitry, it is thought that dendritic cells perform their antigen presenting function to directly activate T-cells within the perivascular spaces of the CNS. Therefore, dendritic cells in the periphery and within the CNS may contribute to the initiation and perpetuation of immune mechanisms germane to the disease process in MS.
Mast cells	Mast cells release granules that are rich in histamine and other inflammatory mediators. Both mast cells and their mediators have been identified in MS lesions. Tryptase, an enzyme uniquely produced by mast cells, is increased in the CSF of MS patients.
Natural killer (NK) cells	Natural killer (NK) cells recognize and kill virally infected cells and tumor cells, and secrete cytokines including IFN-γ, IL-10, IL-5, and IL-13. NK cell numbers are decreased in the CSF and in lesions of MS patients, and cytolytic activity is diminished in comparison to healthy controls. In fact, studies suggest that increases in NK cells in pregnant MS patients may contribute to the decreased disease activity observed during pregnancy and indicate an immunoregulatory role for NK cells in MS.
NK-T cells	NK-T cells are T-cells that express an invariant TCR and some features of NK cells. NK-T cells have been identified in MS lesions and are thought to play a regulatory role in MS, but the conclusions of studies investigating NK-T cell numbers and function in MS patients are conflicting.
γδ T cells	γδ T cells are T lymphocytes that express the invariant γδ T cells receptor and are typically present in high numbers in the epithelium of the gut and are less frequent in the blood. γδ T cells have been identified in MS lesions but their contribution to the pathogenesis of MS has not yet been elucidated.
Non-cellular components	Nitric oxide synthase (NOS) is an inducible enzyme produced by myeloid cells, such as monocytes/macrophages, granulocytes, and dendritic cells, that is used to generate nitric oxide. Nitric oxide is one of several reactive oxygen and nitrogen intermediates that function as potent antimicrobials. NOS is associated with MS lesions, but the role of NOS in MS remains undefined.
CSF = cerebral spinal fluid, IFN = interferon, IL = interleukin, TCR = T-cell receptor, TNF = tumor necrosis factor.	
Source: Reprinted with permission from Frohman TC, O'Donoghue DL, Northrop D (eds). Multiple Sclerosis for the Physician Assistant: A Practical Primer. New York, NY: National Multiple Sclerosis Society; 2011. *Table 1*	

pattern reflective of primary oligodendrocytic dystrophy, similar to that seen with virus- or toxin-induced demyelination. The pattern of demyelination was heterogeneous among different patients, but homogeneous with respect to multiple lesions within the same patient.

The mechanism by which autoreactive T-lymphocytes traverse the blood-brain barrier to initiate inflammation is poorly understood. There is some evidence that early in the disease process there is an increase in adhesion molecules, particularly intercellular adhesion molecule-1 (ICAM-1), on the vascular endothelium of brain and spinal cord. These molecules increase the permeability of the blood-brain barrier and could permit the entry of lymphocytes. Upon entry into the CNS compartment, previously activated T-lymphocytes proliferate and engage myelin-based antigens, triggering the autoimmune inflammatory cascade that leads to demyelination. The release of cytokines activates microglial cells (CNS macrophages), which, in turn, promotes the expression of class II major histocompatibility complex (MHC) molecules and the accumulation of additional cytokines and other inflammatory mediators, such as nitric oxide, free radicals, and superoxide. The net result is a sustained proinflammatory state that destroys myelin, disrupts oligodendrocyte integrity and function, and damages axons.

Table 1 provides an outline of the various components of the innate immune system, with a brief commentary on the role each cell type plays in the pathogenesis of MS [33].

Demyelination impairs nerve impulse transmission and leads to abnormal patterns of nerve conduction, which accounts in large part for the various clinical symptoms and signs of MS. Oligodendrocytes are cells that elaborate the myelin sheath that envelops the axon. During the early, remittent stage of the disease, as inflammation subsides, the number and function of these cells are sufficient to renew the myelin sheath (remyelination) and restore neurologic function. Over time, the repeated inflammatory insults associated with relapsing MS lead to a gradual depletion of functioning oligodendrocytes, and to degenerative changes marked by central scarring within the lesion and focal areas of cerebral atrophy. The clinical correlate is the gradual accumulation of fixed neurologic deficits as the patient with MS transitions to the chronic progressive stage of the disease.

The B-lymphocyte arm of the immune system also contributes to the pathogenesis of MS, especially during the late stages of disease when inflammatory changes are more marked in the gray matter of the brain. In contrast to T-cell mediated inflammation of white matter, myelin-reactive B-lymphocytes and the secretion of myelin-specific antibodies appear to play a significant role in the pathogenesis of gray matter inflammatory injury. The potential mechanisms by which B cells influence pathogenesis include antigen presentation to T cells, autoantibody production, and release of pro-inflammatory cytokines. During periods of active MS inflammation, B-lymphocyte-rich immune cells collect within certain compartments of the CNS, including the meninges; such cell collections, in association with meningeal inflammation, may cause the adjacent subpial cortical demyelination and neurodegenerative features seen in chronic forms of MS [34].

The natural history of the plaque lesion in MS also includes late-developing degenerative features that are irreversible, such as gliosis (scarring), functional abnormalities of damaged axons, neuronal degeneration, and cerebral atrophy.

SIGNS AND SYMPTOMS

The early signs and symptoms of MS are typically mild and difficult to detect. They differ in duration and severity from one individual to another and at different times in the same individual. However, at first clinical presentation, most patients report multiple symptoms. Patients generally experience either acute attacks of neurologic compromise or are afflicted by a steadily progressive deterioration in functional capabilities, as will be discussed in detail later in this course [33].

MS symptoms can be organized into three categories: primary, secondary, and tertiary.

PRIMARY SYMPTOMS

Primary symptoms of MS are caused by the inflammation and demyelination that arises within focal areas of the CNS. The clinical presentation is varied but, in general, consists of some disturbance in vision, sensation, and/or motor function. The most common primary symptoms in patients with MS are:

- Fatigue
- Heat sensitivity
- Muscle spasms
- Dizziness
- Pain
- Paresthesias
- Ataxia
- Cognitive changes
- Visual complaints
- Bowel or bladder dysfunction
- Sexual dysfunction
- Gait problems
- Nausea/vomiting
- Speech problems
- Tremor
- Weakness

Fatigue

Fatigue is the most frequent and characteristic symptom of MS. It typically occurs in the mid-afternoon and may be associated with depression, increased muscle weakness, and drowsiness [35]. Fatigue is disabling in MS, resulting in a patient's inability to participate in daily activities and affecting quality of life and mental health [35].

Heat Sensitivity

Heat sensitivity (also known as Uhthoff phenomenon) is common in most individuals with MS. This occurs when the body becomes overheated due to fever, physical exercise, or exposure to a hot environment, such as hot weather, saunas, and hot baths. It is suspected that the increase in body temperature results in nerve conduction block in central pathways [36; 37]. Patients with MS reach this stage earlier and at comparatively lower temperatures than healthy individuals because nerves are demyelinated. The greater the degree of demyelination, the smaller the necessary increases in temperature to induce symptoms. In individuals with MS, a small increase in body temperature can temporarily result in worsening of neurologic signs and symptoms, including fatigue, cognitive impairment, ataxia, weakness, and urinary incontinence [38].

Spasticity

The majority of patients with MS report some level of spasticity. Painful muscle spasm is experienced by approximately 15% and is often a source of debilitation [39]. Spasticity usually affects the muscles of the extremities (more prominent in the lower extremities than the upper extremities) and can impair an individual's ability to freely move his or her muscles.

Demyelinated nerves are primarily responsible for the spasticity seen in MS, as slowed or interrupted nerve conduction affects the motor function of the muscles. Muscle relaxation is slow and sluggish, and there is involuntary muscle tightening or contraction for long periods or constantly. Amyotrophy of the disuse type can be seen in some patients with MS, usually in the small muscles of the hand.

Dizziness and Vertigo

Approximately 49% to 59% of patients with MS suffer from dizziness or vertigo, and this condition is usually associated with impairment of cranial nerves [40]. In one study, the effects of dizziness were reported to be moderate in 30.9% of patients and severe in nearly 8% [40]. It can substantially impact patients' quality of life, particularly if paired with other symptoms that affect mobility.

Pain

Up to 80% of patients with MS experience varying degrees of pain, and an estimated 50% experience chronic pain [41]. One study found that 63% of patients with MS reported one or more painful symptoms [39]:

- Headache (43%)
- Neuropathic extremity pain (26%)
- Back pain (20%)
- Painful spasms (15%)
- Lhermitte sign (16%)
- Trigeminal neuralgia (3.8%)

MS pain is mainly neuropathic—the result of nerve damage and faulty conduction—and can include stabbing, burning, and shock-like sensations (e.g., allodynia, dysesthesias, paresthesia). Lhermitte sign is often considered a classic sign of MS and consists of a brief, electric shock-like sensation that runs down the spine and is triggered by bending the neck forward or backward.

Some patients will experience musculoskeletal pain, likely the result of immobility and gait problems. Patients with spasticity are at greater risk for this type of pain.

Impaired Cognition

Approximately 40% to 70% of patients with MS experience varying degrees of cognitive impairment [42]. This may manifest as decreased capacity for concentration or memory and slowed thinking. Severe cognitive impairment can significantly impact patients' ability to carry out activities of daily living.

Vision Problems

Impaired vision is frequently present in patients with MS, most commonly unilateral optic neuritis, which is present in approximately in 66% of cases [43]. Optic neuritis usually manifests as acute or subacute unilateral eye pain that increases with eye movements [44]. It can also lead to blurring or graying of vision or blindness in one eye. However, while unilateral optic neuritis is common in MS, simultaneous bilateral optic neuritis (resulting in total blindness) is rare [43]. Approximately 90% of patients with MS regain normal vision over a period of two to six months after an acute episode of optic neuritis [43].

Patients may also present with intranuclear ophthalmoplegia (INO), a condition characterized by impaired nystagmus and defective horizontal ocular movements of the abducting eye. This type of visual impairment is caused by a lesion of the medial longitudinal fasciculus on the side of diminished adduction. When present in young patients, bilateral internuclear ophthalmoplegia is suggestive of MS [43].

Sensory Symptoms

Patients with MS often experience various sensory symptoms through the course of the disease. This includes impairment of vibration and joint position sense, decreased pain and light touch perception, "pins-and-needles" sensation, tightness, and coldness of the extremities. A dysesthetic itching specifically present around the cervical dermatomes is indicative of MS.

Bowel, Bladder, and Sexual Dysfunction

The severity of bowel sphincter impairment and sexual dysfunction is directly proportional to the extent of motor impairment in the lower extremities. Urgency is the most frequent urinary complaint in patients with MS, with frequent urinary incontinence common as the disease progresses. MS can also lead to atonic dilated bladder. Upper and lower motor neuron impairment can result in constipation. Erectile dysfunction is common in men suffering from MS. As many as 91% of men and 72% of women with MS report some form of sexual dysfunction [45].

Gait Imbalance

Gait disturbances and imbalance are characteristic symptoms of MS. Patients will experience varying degrees of difficulty executing coordinated actions because of damaged cerebellar pathways. Dysmetria and hypotonia are frequently seen in the upper extremities. Some patients exhibit intention (cerebellar) tremor, particularly in the head and limbs. These tremors can be incapacitating and refractory to treatment. Walking is also affected due to truncal ataxia. In severe cases, patients lose the ability to stand (astasia).

Paroxysmal Symptoms

Patients with MS frequently exhibit paroxysmal attacks of motor or sensory symptoms causing facial paresthesia, trigeminal neuralgia, ataxia, and diplopia. Dystonia (painful tonic contractions of muscles) is seen when the motor system is involved.

SECONDARY SYMPTOMS

Secondary symptoms arise as a result of the presence of certain primary symptoms. For example, pressure ulcers may form as a complication of paralysis, a primary symptom. Bladder problems or urinary incontinence can cause frequent, recurring urinary tract infections. These symptoms are treatable, but ideally, they should be avoided by treating the primary symptoms. The most common secondary symptoms present in patients with MS are [46]:

- Urinary tract infections
- Kidney or bladder stones
- Pressure ulcers
- Muscle contractures
- Respiratory infections
- Poor nutrition
- Difficulty breathing (severe)
- Disuse weakness
- Poor postural alignment and trunk control
- Decreased bone density
- Back pain

TERTIARY SYMPTOMS

Tertiary symptoms may be described as the "trickle down" effects of MS and include the social, psychological, and vocational complications associated with the primary and secondary symptoms [46]. Depression is a frequent tertiary symptom present among people with MS. Social isolation, job loss, marital or interpersonal conflict, and anxiety may all develop as a result of various primary and secondary symptoms of MS.

DISEASE ONSET AND CLINICAL SUBTYPES

In a given case, the onset and subsequent course of MS tends to follow one of four commonly observed clinical patterns (subtypes or phenotypes). Because accurate definitions and clinical course descriptions are important for purposes of communication, clinical trial design, and prognostication, an international panel of MS experts provided the first standardized descriptions of MS subtypes in 1996 [47]. In 2013, the International Committee on Clinical Trials of MS revised the definitions and clinical descriptors to more accurately reflect recently identified clinical aspects and imaging findings of the disease [48]. The 2013 revision classifies the four basic MS disease phenotypes as: clinically isolated syndrome, relapsing remitting, secondary progressive, and primary progressive [49].

CLINICALLY ISOLATED SYNDROME

Clinically isolated syndrome is a first episode of neurologic symptoms suggestive of MS but lacking clear confirmation of the diagnosis. The episode must last more than 24 hours. Symptoms may be unifocal or multifocal, and MRI may show subtle structural changes in the brain or spinal cord indicative of inflammatory demyelination [49]. This constellation of findings constitutes evidence for, but not confirmation of, the diagnosis of MS, as persons who present with a clinically isolated syndrome may or may not go on to develop MS [49]. In such cases, the patient is identified as someone possibly at risk of developing MS in the future. A cerebrospinal fluid analysis combined with MRI may be helpful in predicting likelihood of conversion to MS [49]. Some studies have shown that starting a disease-modifying treatment at this stage may delay both conversion to MS and onset of the progressive phase [50].

RELAPSING-REMITTING

Relapsing-remitting multiple sclerosis (RRMS) is characterized by alternating series of clearly defined clinical relapses (or exacerbations) followed by periods of partial or complete recovery (remissions). RRMS affects young adults, is three times more common in women than men, and accounts for about 85% of all cases of MS [51]. Functional and structural impairments suffered during relapses may either resolve or leave sequelae.

The majority of patients with RRMS subsequently enter a secondary progressive disease course. Studies have demonstrated that the time from RRMS onset to secondary progression is approximately 20 years [51]. A minority of patients with RRMS will have a relatively benign course.

The most frequent symptoms of RRMS include [51]:

- Episodes of visual loss or double vision
- Tingling or numbness
- Fatigue
- Urinary urgency
- Balance problems
- Weakness

SECONDARY PROGRESSIVE

Following an initial relapsing-remitting course, most patients with RRMS eventually transition to a secondary progressive pattern of MS (SPMS), characterized by fewer clinical relapses and a slowly progressive course of neurologic impairment without any well-defined periods of remission [47]. Of patients diagnosed with RRMS who do not receive treatment, 50% will develop SPMS within 10 years and 90% will progress to SPMS within 25 years [52]. Conversion of RRMS to SPMS is determined solely on clinical findings; biochemical markers or specific tests are not useful.

Persons with SPMS usually experience cognitive impairment, pain, and numbness. One of the characteristic features of SPMS is disabling tremor that can last for an extended period of time. This disease is characterized by a progressive deterioration of ability, and people with SPMS usually do not recover completely from a relapse.

PRIMARY PROGRESSIVE

Primary progressive MS (PPMS) is characterized by steady disease progression from the onset of symptoms, perhaps with occasional remissions and temporary minor improvements [47]. Approximately 10% to 15% of patients with MS carry the diagnosis of PPMS [49]. Patients diagnosed with PPMS tend to be older (mean age: 40 years) than those with RRMS, and there is no gender difference in incidence [49].

In PPMS, there is a progressive decline in function with an absence of acute inflammatory attacks. Patients exhibit steadily worsening motor dysfunction and increased disability. There is no established disease-modifying therapy for PPMS, which carries a worse prognosis for disability than does RRMS [53]. Disease-modifying therapies work primarily by reducing inflammation in the CNS. They do not work as well in a disease course that is characterized by nerve degeneration rather than inflammation. For this reason, they have not been shown to be effective in progressive forms of MS unless the patient relapses or has demonstrated MRI activity caused by inflammation [53]. Patients with PPMS may experience symptoms similar to those seen with RRMS. However, PPMS usually involves the spinal cord, and signs and symptoms are often related to spinal involvement. Approximately 80% of patients with PPMS have progressive weakness of the lower limbs with spasticity, known as spastic paraparesis [54]. Approximately 15% of patients with PPMS experience ataxia as a result of progressive cerebellar involvement. Other symptoms include altered sensation, muscle spasms and weakness, mobility problems, difficulty in speech or swallowing, visual impairments, fatigue, pain, and bladder and/or bowel difficulties. An estimated 6% of patients with PPMS suffer from hemiparesis [54].

The lesions associated with PPMS show a reduction in the number of oligodendrocytes and myelin repair when compared to other types of MS. Widespread inflammation with diffuse axonal damage in white brain matter is often present. This leads to cortical tissue and axonal damage, with associated irreversible and progressive disability. There is increased intrathecal production of IgG antibodies, and oligoclonal bands are found in the CSF of approximately 90% of cases [54].

UNCOMMON SUBTYPES

Progressive Relapsing

In a small subset of patients (less than 5%), the disease course is reflective of a mixed pattern, defined in the past as progressive-relapsing MS (PRMS), and characterized by a steady progression of clinical neurologic damage with clear acute exacerbations (with or without full recovery) and no total remissions [47]. Disease progression continues between relapses, leading to the permanent loss of neurologic function and cumulative disability. PRMS is associated with a severe disease course and a relatively high mortality rate.

Benign MS

Benign MS is a retrospective diagnosis characterized by long-term absence of symptoms with no functional impairments of neurologic systems 15 years after the disease onset. Approximately 15% of patients with an acute MS attack do not experience another relapse [55]. However, a relapse may occur after many years of inactivity, and it important not to assume that mild MS is truly benign.

Malignant MS

Malignant MS (also known as Marburg variant) is characterized by a rapidly progressive course resulting in major disability and usually death within one year of the onset. This disease course is most common in children, although older adults may be affected as well.

Malignant MS is associated with larger lesions, more often involving the brainstem. It shows poor response to treatment, but there may be some improvements with plasmapheresis or experimental therapies (e.g., stem cell transplantation).

Late-Onset MS

On occasion, a patient presents with new-onset MS at an unexpectedly late or early stage in life. Such cases are categorized as either late- or early-onset disease. These types of MS tend to have an atypical presentation and to follow a less predictable clinical course.

Late-onset MS is diagnosed in patients older than 50 years of age. Because many of the signs of late-onset MS are similar to other medical conditions associated with aging, misdiagnosis or delayed diagnosis is common. Late-onset MS is characterized by a progressive course, predominant motor symptoms, difficulties with treatment, and poor prognosis.

Some of the most frequent motor symptoms present in late-onset MS include:

- Gait disturbances
- Trouble moving arms and/or legs
- Muscle spasms
- Tremor
- Clumsiness
- Weakness

Most patients with late-onset disease experience only one symptom in the beginning and steadily accumulate more symptoms. The disease typically follows a primary-progressive course and is associated with poorer response to treatment than the relapse-remitting types seen more often in early-onset. Patients with late-onset MS frequently have memory and learning disabilities, difficulty with selective attention, and short-term memory deficits. Depression is also common. Disability progression appears to be faster and more severe in late-onset MS.

Early-Onset MS

Early-onset MS is usually diagnosed in patients younger than 20 years of age. It accounts for approximately 0.4% to 10.5% of all MS cases [56]. Usually, the disease is characterized by a relapsing-remitting course, a high recovery rate from initial attack, and a long remission and slow progression rate. Sensory symptoms are more common than motor symptoms in these patients, and vision loss (optic neuritis) is a common initial presentation. Other functional systems are involved with a variable frequency. Seizures, malaise, irritability, and low-grade fever may also be present.

DIAGNOSIS

Diagnosis of MS can be difficult, as initial signs and symptoms may be nonspecific or mimic other neurologic disorders. Careful and repeated neurologic examination and selected diagnostic testing over time may be required to confirm the diagnosis. During the course of evaluation, it is important to assess for clinical subtype, form a judgment as to certainty of the diagnosis, and define the extent of disability. The basic requirements for the diagnosis of MS include neurologic symptoms and signs compatible with the diagnosis; evidence of "dissemination in time" (sequential or relapsing symptoms) and "dissemination in space" (two or more lesions on MRI at different sites in the CNS); and no alternative explanation/diagnosis for the clinical and imaging findings [57].

There is no single test or gold standard for the diagnosis of MS. The process of reaching a diagnosis typically involves [57]:

- Evidence from the patient history
- Clinical examination
- One or more laboratory tests and neuroimaging studies

All three of these approaches are generally necessary in order to accurately diagnose MS and complete the differential diagnosis.

The diagnosis of MS often requires assessment at multiple phases of the clinical course [57]. Patients often experience varying degrees of neurologic dysfunctions at different stages, resulting from disease flares within varying regions of the brain or spinal cord. The diagnosis of MS must be concluded by careful assessment of all the evidence both for and against the disease. Final diagnosis will depend upon the extent to which the patient's overall picture has the expected findings typical of MS.

NEUROLOGIC EXAM

A thorough and accurate neurologic examination should be conducted to assess:

- Cranial nerve function
- Coordination
- Strength
- Reflexes
- Sensation

A variety of neurologic exam techniques are useful to evaluate the many areas in which dysfunction may be present (***Table 2***). Because no particular neurologic symptoms or findings are pathognomonic for MS, this process can be lengthy. Certain important clues from the history and/or physical exam often lead to the correct diagnosis. It is important to take into account, and prepare for, any cultural or language barrier to effective communication with the patient. When there is an obvious disconnect in the communication process between the practitioner and patient, an interpreter is required.

INO, especially a bilateral INO in young patients, is suggestive of MS, as it is rare in other conditions. Altered color vision, unilateral optic pallor, and/or Marcus-Gunn pupil may be indicative of optic neuritis. Patients with MS may also exhibit nystagmus.

A mild intention tremor can be an early sign of MS. Patients with early MS may also exhibit a positive Romberg sign, or decreased vibratory and proprioceptive sense in lower extremities. A positive Lhermitte sign in an adult younger than 60 years of age may indicate MS [58].

For some patients, clinical symptomatology and neurologic exam findings are inconclusive, especially in individuals who have experienced separate episodes of neurologic symptoms [58]. As such, additional diagnostic tests may be necessary to fully evaluate the patient and determine the diagnosis. This can include imaging, laboratory tests, and nerve stimulation.

MAGNETIC RESONANCE IMAGING

Plaque lesions (foci of inflammation and demyelination) of MS are best detected using MRI of the brain or spinal cord. MRI will demonstrate the presence, location, number, and size of MS lesions. MRI is also important in excluding other pathologic diagnoses. It is used for diagnostic purposes and to monitor the course of disease and response to therapy. Most patients with symptomatic MS have demonstrable lesions, and MRI often reveals multiple lesions, even in patients with the clinically isolated syndrome [33; 57]. MRI with contrast enhancement (i.e., IV gadolinium) provides a better assessment of active inflammation within plaques and, by elimination, can reveal the presence of older lesions not associated with current symptoms [58; 59]. If present, these older lesions provide some evidence of a period of occult disease prior to the onset of symptoms. As MRI techniques become more sophisticated and pathologically specific, there is an increased likelihood of exploring the pathologic classification of MS.

NEUROLOGIC SIGNS AND TESTS		
Test	**Description**	**Notes**
Romberg test	Patient stands erect with feet together and eyes closed. Swaying or falling is considered positive.	Used for patients with ataxia. Indicates loss of proprioception.
Lhermitte sign	Patient bends the head forward or clinician puts pressure on the posterior cervical spine. An electrical shock sensation is considered positive.	Used to determine the presence of lesions on the cervical spine. Often considered a classic finding in MS but can be caused by a number of conditions.
Gait tests	Observe patient walking normally, walking heel-to-toe, and walking on only toes/heels. Any abnormalities should be noted.	This test evaluates ataxia in various parts of the body.
Point-to-point movement evaluation	Patients alternate touching their extended index finger to their nose and the examiner's outstretched finger.	These are tests to evaluate ataxia, dysmetria, and cerebellar dysfunction. Positive findings are indicative of loss of motor strength, loss of proprioception, or a cerebellar lesion.
	Supine patient places right heel on left shin just below the knee and slides it down to the top of the foot as quickly as possible without making mistakes. Repeat on opposite side. Inability to complete quickly is considered positive.	
Visual acuity and color tests	Patient reads letters from a board to assess visual acuity and from the Ishihara Color Vision Test to assess color vision. Inability to distinguish figures is considered positive.	These tests evaluate for the presence of optic neuritis, perhaps the most frequent symptom in MS.
Babinski sign	The lateral side of the sole of the foot is lightly stimulated from the heel along a curve to the toes. If the hallux dorsiflexes and the other toes fan out, this is considered a positive Babinski sign.	These tests evaluate for signs of disease process in the motor neurons of the pyramidal tract. They are positive in individuals with neurologic problems of the corticospinal tract, including those with MS.
Chaddock sign	Similar to Babinski's sign, this test involves stimulation over the lateral malleolus rather than the bottom of the foot. A positive response elicits an extensor response similar to Babinski sign.	
Hoffman reflex	Clinician taps the nail or flicks the terminal phalanx of the middle or ring finger. A positive response is seen with flexion of the terminal phalanx of the thumb.	This test evaluates problems in the corticospinal tract. However, it is also positive in hyper-reflexive patients. Findings that are acute or asymmetrical are more indicative of disease.
Halmagyi-Curthoys head impulse test	Clinician randomly moves the patient's head side to side. If the eyes remain stationary while the head is moved, this is considered positive.	Test reveals dissociation between movement of the eyes and of the head. Indicative of peripheral vestibular disease.
Perception tests	A monofilament, tuning fork, or pin is applied to patient's body. Ability to perceive the touch or vibration is considered positive.	Evaluates the level of sensory perception in certain parts of the body.
Muscle strength tests	Patient attempts to resist pressure applied by the clinician to various muscle groups. Level of resistance can be rated on a scale from none to normal strength.	Patterns of weakness can help localize a lesion to a particular cortical or white matter region, spinal cord level, nerve root, peripheral nerve, or muscle. Differences in strength between left and right sides are easier to evaluate than symmetrical loss unless the weakness is severe.
Reflexes	This is done with both ends of the hammer. The reflexes can be normal, brisk (i.e., too easily evoked), or non-existent.	—

Source: Compiled by Author *Table 2*

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the International Panel on Diagnosis of Multiple Sclerosis, brain and spinal cord MRI remain the most useful paraclinical tests to aid the diagnosis of multiple sclerosis and can substitute for clinical findings in the determination of dissemination in space and/or time in patients with a typical clinically isolated syndrome.

(https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(17)30470-2/fulltext. Last accessed December 12, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

In 2018, the Consortium of MS Centers (CMSC) published revised MRI protocol and clinical guidelines for the diagnosis and follow-up of MS [60]. A 2021 revision of previous guidelines on MRI use for patients with MS merged recommendations from the Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS) study group, CMSC, and the North American Imaging in Multiple Sclerosis Cooperative (NAIMS) [61]. In addition to emphasizing the value of three-dimensional (3D) acquisition techniques, the MAGNIMS-CMSC-NAIMS consensus group extends recommendations for the use of MRI in patients with MS to MS in childhood, during pregnancy, and in the postpartum period [61].

A brain MRI with gadolinium is recommended for the diagnosis of MS. If the brain MRI is non-diagnostic, or if presenting symptoms are referable to the spinal cord, then a spinal cord MRI is recommended [60; 61]. Follow-up brain MRI is recommended for the following clinical purposes [60]:

- To demonstrate "dissemination in time" for confirmation of diagnosis
- To detect clinically silent disease activity while on treatment
- To evaluate unexpected clinical worsening
- To reassess the original diagnosis or as a new baseline MRI before modifying therapy
- Every six months to two years for patients with relapsing MS

Small amounts of gadolinium-based contrast agents do accumulate in the brain of some persons who have received multiple doses. Although there is no current evidence that these deposits are harmful, the Consortium protocol and the MAGNIMS-CMSC-NAIMS consensus recommendations emphasize that gadolinium should be used judiciously [60; 61]. Gadolinium-based contrast is helpful but not essential for detecting subclinical disease activity. In addition to evaluating the patient with clinically isolated syndrome, the use of a gadolinium-based contrast agent is recommended in patients with highly active disease and when there is rapid onset of unexplained and unexpected clinical worsening [60; 61].

On occasion, MRI performed on a patient without overt or significant symptoms will demonstrate abnormalities suspicious for MS, based on location and morphology within the CNS [58]. These cases are classified as the "radiologically isolated syndrome," and follow-up studies have shown that the majority of such patients eventually develop more lesions and progress to a true clinical MS exacerbation. These patients likely represent an early, preclinical stage of MS, identified by MRI in the course of evaluation for other reasons [33].

When there is a weak association between common neuroradiologic markers of MS and clinical disability, this is referred to as a clinicoradiologic paradox. This partly relates to the principle of eloquence and non-eloquence. Non-eloquent lesions are lesions that tend to develop in particular anatomic locations and are not always associated with clinically consistent symptoms; they are also referred to as silent or subclinical. Eloquent lesions usually develop in particular anatomic locations or pathways and almost always result in the manifestation of a characteristic inflammatory demyelinating syndrome [33]. These lesions are associated with expected clinical neurologic manifestations (***Table 3***).

A number of MRI sequences are done to reveal different histopathologic features of the MS plaque. These MRI sequences are "weighted" to demonstrate water or fat. T1-weighted, T2-weighted, and proton-density scans are used in the diagnosis of MS, and all are sensitive to the higher-than-normal water content found in MS lesions. These images are partially confounded by the intense signal of the water content of the CSF. 3D fluid-attenuated inversion recovery imaging is an imaging technique that nulls fluids and is used to suppress CSF effects and enhance the periventricular hyperintense lesions present in MS [62]. The use of 3D acquisition techniques is preferred to two-dimensional acquisitions, as 3D techniques have become more routinely available on clinical scanners. They also improve lesion detection and the realignment of anatomic orientation that is necessary to detect new lesions when comparing serial MRI scans [61]. 3D techniques also are more sensitive in depicting lesions in cortical and infratentorial locations than dual-echo sequences [63].

MRI of the brain in a patient with MS typically shows multifocal T2-hyperintense white matter lesions in characteristic locations. Spinal cord lesions, most commonly in the cervical region, are seen in about half of patients at first presentation and in 80% to 90% of patients with established MS [2]. The scan is considered strongly predictive of MS if it shows at least four lesions in the brain or three lesions with at least one present in the periventricular region. However, while these criteria are considered sensitive, they are not very specific. More accurate criteria require at least three lesions be present, fulfilling at least two of the following criteria:

ELOQUENT MS SYNDROMES		
Eloquent Syndrome	**Localization**	**Clinical Manifestations**
Optic neuritis	Optic nerve	Visual acuity loss Visual field suppression Color desaturation Pain Relative afferent pupillary defect
Internuclear ophthalmoparesis (INO)	Medial longitudinal fasciculus (MLF)	Slowing of adducting eye movements Diplopia Oscillopsia
Skew deviation	Otolith pathways	Vertical or oblique diplopia Subjective deviation of visual vertical
Cranial nerve palsies	Brainstem	Facial weakness Facial numbness (cranial nerve V) or pain Diplopia (cranial nerves III, IV, VI) Vestibulopathy (cranial nerve VIII or nucleus)
Rubral tremor	Superior cerebellar peduncle	Tremor
Ataxia	Cerebellum	Instability and reduced postural control
Trigeminal neuralgia	Trigeminal system	Paroxysmal facial pain
Myelitis	Spinal cord	Sensory disturbances Spasticity Bowel/bladder/sexual dysfunction Weakness

Source: Reprinted with permission from Frohman TC, O'Donoghue DL, Northrop D (eds). Multiple Sclerosis for the Physician Assistant: A Practical Primer. New York, NY: National Multiple Sclerosis Society; 2011. *Table 3*

- Periventricular lesion
- Lesion at least 6 mm in diameter
- Infratentorial lesion

T1-weighted, T2-weighted, and proton-density scans also reveal complementary information about the nature of MS. T1-weighted scans provide a better anatomical picture of the brain and are useful for detecting older lesions and abnormal areas. These scans are often used with contrast to illuminate areas of recent inflammation that may be associated with active MS. T2-weighted scans do not show the best anatomical picture of brain compared to T1-weighted scans, but they can detect both new and old lesions. These scans are repeated over a period of time to track the development of MS. Proton-density scans also detect both old and new lesions and are particularly useful in detecting periventricular plaques.

High-field and ultra-high-field MRI can detect a greater number and volume of T2-hyperintense and gadolinium-enhancing brain lesions than those operating at lower fields [64; 65]. These high-power MRIs can detect MS at a very early stage and are more sensitive to cortical lesions [66].

The diverse disease processes associated with the subtypes of MS can be detected by MRI as well. In PPMS, MRI will show small lesions that do not enhance with a contrast agent, indicating little or minimal inflammation. This particular characteristic is a clear differentiation from relapsing-remitting disease. The severity and extent of the physical symptoms of MS can be confirmed by visualization of the anatomic location of lesions within the CNS. For example, a lesion present in the spinal cord may result in numbness in the limbs and bladder disturbance. Lesions in the optic nerve are usually responsible for optic neuritis, leading to blurred vision and a loss of color perception.

There is a correlation between the "lesion load" (i.e., total volume of CNS tissue affected by the MS disease process) and the probability that a key part of the brain or spinal cord will be affected, resulting in clinical symptoms. However, studies have demonstrated only weak correlation between MRI lesion load and age at disease onset, disease duration, and progression [67]. MRI lesion burden is not considered a good indicator of disease progression, especially in cases of advanced MS.

MS lesions found in the spinal cord usually give rise to identifiable symptoms and are highly eloquent of the disease process; new spinal MS lesions are strongly correlated to new clinical manifestations. Approximately 75% of patients with MS have lesions within the spinal cord, principally the cervical cord, and most spinal cord lesions are located in the dorsal columns [68]. These lesions are usually oval or cigar-shaped and can span one or two vertebral segments (referred to as skip lesions).

Advances in MRI Imaging

Despite its many advantages, the principal handicap of MRI is its low sensitivity in detecting grey-matter involvement and diffuse damage in white matter. Advances made in conventional and non-conventional MRI methods are enabling better assessment of CNS tissue damage in patients with MS. New techniques that can provide more insight into MS include:

- Proton magnetic resonance spectroscopy (1H-MRS)
- Magnetization transfer imaging
- Diffusion imaging
- Functional MRI
- Optic-nerve imaging
- Spinal-cord imaging
- Myelin water fraction (MWF) imaging
- Perfusion MRI
- Ultra-high-field MRI

MRI assessment of lesions on noncontrast T1- and T2-weighted images and on gadolinium-enhanced T1-weighted images provides an important imaging tool for close monitoring of the disease course [69]. However, conventional MRI is weakly correlated with clinical status of MS and has low sensitivity [70; 71]. New approaches in the field of data management and post-processing have the potential to change the way MS is diagnosed currently. With the help of serial analysis of images, it is now possible to detect a shift in the patient's disease from more inflammatory to more degenerative pathologic processes. This shift may be indicative of possible atrophy and clinical disability [72]. Another method called subtraction imaging displays changes over time between two scans in a single map [73]. This method is more sensitive to lesion evolution compared to conventional techniques.

Voxel-based morphometry is a novel method that explores the association between regional patterns of atrophy and particular functional impairment [74; 75]. Researchers are searching for a method that delineates the relationship between regional atrophy and white matter tract damage and the resulting clinical implications. Diffusion tensor MRI technique has the potential to map the white-matter architecture in details. This novel technique can then be used to correlate quantitative measures of CNS tissue damage and its functional significance, leading to more clinically relevant assessment of the burden of disease.

Grey matter damage in MS occurs largely independent of white matter lesions and shows stronger correlation with clinical parameters than white matter damage. One meta-analysis used differential mapping to assess global and regional grey matter volume differences in MS [76]. Potential effects of disease duration and degree of functional disability also were analyzed. A highly localized pattern of regional grey matter volume loss was observed in RRMS, and grey matter volume loss in left pre- and postcentral regions correlated with increased functional disability [76].

Newer MRI contrast agents composed of iron particles (i.e., nano-size particles of iron oxide or superparamagnetic iron oxide particles) are being used in patients with MS to track macrophages [77; 78]. Studies using these agents have confirmed a mismatch of MRI enhancement, signifying heterogeneity of the underlying MS pathology [77; 78]. Tracking macrophages with these tiny iron particles can help monitor the efficacy of drugs in MS treatment. Gadofluorine M, a gadolinium-based MRI contrast agent, is very sensitive in the detection of inflammatory CNS lesions, as it selectively accumulates in nerve fibers undergoing Wallerian degeneration [79].

1H-MRS

1H-MRS can be used to measure N-acetylaspartate levels to monitor CNS damage. Levels of choline-containing compounds usually increase during myelin breakdown, remyelination, and inflammation. 1H-MRS is helpful in detecting levels of glutamate, glutamine, and gamma-aminobutyric acid (GABA), and advances in 1H-MRS techniques could revolutionize the diagnosis of MS.

Magnetization Transfer MRI

Another nonconventional technique, magnetization transfer MRI, can detect the magnetization transfer ratio (MTR), which helps in monitoring disease progression in patients with MS. A low MTR indicates damage to neurons, particularly myelin and axonal membranes. Decreased MTR is particularly pronounced in patients with the progressive forms of MS and has a tendency to deteriorate over time [80]. Studies have demonstrated that this technique has prognostic value for subsequent disease evolution [80].

Diffusion MRI

Diffusion MRI is helpful in noninvasively mapping the diffusion process of molecules in biologic tissues and can detect focal MS lesions. Research is focusing on the role of direct MRI detection of neuronal activation, either by diffusion-weighted imaging or by the effect that neuronal currents have on a local, externally applied magnetic field [81; 82]. In the future, this technique could provide vital information about the disease processes of MS and the effects of these processes on motor and cognitive function. Diffusion tensor imaging (DTI) is useful in evaluating normal-appearing white matter and other lesions in MS that are difficult to evaluate with routine MRI. Advanced diffusion MRI is capable of capturing in vivo microstructural changes in the brain and spinal cord in both normal and pathological states in greater detail than DTI [83]. Another advanced MRI technique, diffusion basis spectrum imaging, shows differences between MS subtypes related to the severity and composition of underlying tissue damage [84].

Functional MRI

Functional MRI, or fMRI, measures brain activity by detecting the changes in blood oxygenation and flow that occur in response to neural activity. fMRI uses the blood-oxygen-level-dependent contrast mechanism and may be useful in

detecting alterations in visual, cognitive, and motor networks in patients with MS.

Myelin Imaging

Research on MS has emphasized the need to develop MRI techniques that can measure the invisible burden of disease in the CNS and establish highly sensitive and specific markers of disease progression. Myelin-selective MRI is a promising technique that allows accurate mapping of MWF, a parameter that is linked to brain white matter myelination [85]. Studies suggest that a 30% to 50% decrease in MWF occurs in MS lesions and a 7% to 15% decrease is seen in normal-appearing white matter in patients with MS [86; 87].

OPTIC-NERVE IMAGING

Imaging of the optic nerves is difficult because of the limited resolution of MRI and patient motion artefacts. However, optic neuritis can be an excellent model to understand the pathophysiology of MS. A link has been observed between acute inflammation and conduction block in optic neuritis [88]. Dynamic MTR changes indicate myelin damage and repair due to axonal degeneration and demyelination [89].

Optical coherence tomography shows promise as a potential marker of axonal loss in assessing neurodegeneration in MS [90; 91]. This technique can detect thinning of the retinal nerve fiber layer.

CEREBROSPINAL FLUID ANALYSIS

Performing lumbar puncture for CSF analysis is not essential for confirming diagnosis of MS; however, it can be helpful in the differential diagnosis. CSF analysis can detect intrathecal synthesis of antibodies, which is evident by the presence of oligoclonal bands, IgG index elevation, and an increased IgG synthesis rate. It is important to note that the presence of oligoclonal bands in CSF is suggestive of MS, but its presence in serum is not. CSF analysis should always be interpreted with regard to the clinical situation.

Oligoclonal bands are found in the CSF of approximately 75% to 85% of patients with MS [58; 92]. However, a similar pattern of antibody synthesis is present in various types of infectious, inflammatory, vascular, neoplastic, and paraneoplastic conditions as well. Conditions other than MS are considered when CSF analysis reveals pleocytosis (>50 white blood cells/mm^3) or a CSF protein concentration greater than 100 mg/dL [93].

Detection of oligoclonal bands in CSF by isoelectric focusing is the most sensitive laboratory test for MS and the most sensitive predictor of conversion from clinically isolated syndrome to MS. It is also the best test to show local intrathecal IgG synthesis. Patients with suspected MS who lack oligoclonal IgG bands in CSF should be investigated for other diagnoses, although it is important to remember that not all patients with MS display oligoclonal bands. Studies have demonstrated that the frequency of oligoclonal bands in the CSF of patients with MS varies in different regions of the world, with higher rates in Northern Europe and North America and lower rates in Asia [93].

The association between the presence of oligoclonal bands in CSF and progression of disability in MS is not yet clear. However, one literature review found that the presence of both IgG and IgM bands are associated with a worse MS prognosis [94]. The oligoclonal band pattern in CSF does not change during the course of the disease, but banding patterns do vary among patients.

EVOKED POTENTIAL TESTING

Evoked potential testing consists of electrical tests of the nerve pathways, which are less responsive to stimulation in individuals with MS. This noninvasive and sensitive test checks brain responses by visual- and sensory-evoked potentials, identifying CNS lesions or damaged areas.

There are three main types of evoked potential tests used in the diagnosis of MS:

- Brainstem auditory evoked potentials: A series of clicks played in each ear via headphones
- Visual evoked potentials: A series of alternating checkerboard patterns shown on a screen
- Somatosensory evoked potentials: Short, mild electrical shocks administered to a patient's arm or leg

The patient's responses are analyzed carefully for response size and the speed in which the brain receives the signal. Demyelination can be indicated by weak or slow brain response to the test, suggesting possible MS.

Only results of visual evoked potentials are considered part of the diagnostic criteria for MS. Visual evoked potentials can detect sluggish neurotransmission along the optic nerve pathways, a finding common in individuals with asymptomatic MS. However, a positive finding on evoked potential testing is not specific to MS, and the abnormalities detected may also be present in other conditions.

DIAGNOSTIC CRITERIA

The McDonald criteria established by the International Panel on the Diagnosis of MS are used to determine both diagnosis and subtype of MS based on brain imaging, extent of symptoms, and duration of symptoms (***Table 4***) [58]. These criteria were first introduced in 2001 and were most recently revised in 2017 [95].

The 2010 revision of the McDonald criteria improved the sensitivity from 46% to 74%, with a slight tradeoff in specificity (decreased from 94% to 92%) [58]. Major changes in the 2010 revision included simplification of the demonstration of CNS lesions in space and time through MRI imaging and consideration of application to non-Western White populations [58].

The 2017 modification of the McDonald criteria focused on differentiating those patients with clinically isolated syndrome who have a high probability of incipient MS and therefore would benefit from early introduction of disease-modifying therapy. The 2017 revision eliminates the requirement for dissemination in time to diagnose MS in patients with a typical

2017 MCDONALD CRITERIA FOR THE DIAGNOSIS OF MS	
Clinical Presentation	**Additional Data Needed for MS Diagnosis**
In a patient with a typical attack/CIS at onset	
≥2 attacks[a]; objective clinical evidence of ≥2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack[b]	None[c]
≥2 attacks[a]; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: ≥1 symptomatic or asymptomatic T2 lesion in at least 2 MS-typical regions of the CNS (periventricular, juxtacortical/cortical, infratentorial, or spinal cord)[d]; or await a further clinical attack[a] implicating a different CNS site
1 attack[a]; objective clinical evidence of ≥2 lesions	CSF-specific (i.e., not in serum) oligoclonal bands Dissemination in time, demonstrated by: Simultaneous presence of asymptomatic or symptomatic gadolinium-enhancing and nonenhancing lesions at any time; or a new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or await a second clinical attack[a]
1 attack[a]; objective clinical evidence of 1 lesion (clinically isolated syndrome)	Dissemination in space and time, demonstrated by: For dissemination in space: ≥1 symptomatic or asymptomatic T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical/cortical, infratentorial, or spinal cord)[d]; or await a second clinical attack[a] implicating a different CNS site For dissemination in time: Simultaneous presence of symptomatic or asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or a new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or await a second clinical attack[a]
In a patient with progression of disability from onset	
Insidious neurologic progression suggestive of MS (primary progressive)	1 year of disease progression (retrospectively or prospectively determined) plus two of the following three criteria[d]: • Evidence for dissemination in space in the brain based on ≥1 symptomatic or asymptomatic T2 lesions in the MS-characteristic (periventricular, juxtacortical/cortical, or infratentorial) regions • Evidence for dissemination in space in the spinal cord based on ≥2 T2 lesions in the cord • Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

If the criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is MS. If suspicious, but the criteria are not completely met, the diagnosis is possible MS. If another diagnosis arises during the evaluation that better explains the clinical presentation, then the diagnosis is not MS.

[a]An attack (relapse, exacerbation) is defined as patient-reported or objectively observed events typical of an acute inflammatory demyelinating event in the CNS, current or historical, with duration of at least 24 hours, in the absence of fever or infection. It should be documented by contemporaneous neurologic examination, but some historical events with symptoms and evolution characteristic for MS, but for which no objective neurologic findings are documented, can provide reasonable evidence of a prior demyelinating event. Reports of paroxysmal symptoms (historical or current) should, however, consist of multiple episodes occurring over not less than 24 hours. Before a definite diagnosis of MS can be made, at least 1 attack must be corroborated by findings on neurologic examination, visual evoked potential response in patients reporting prior visual disturbance, or MRI consistent with demyelination in the area of the CNS implicated in the historical report of neurologic symptoms.

[b]Clinical diagnosis based on objective clinical findings for 2 attacks is most secure. Reasonable historical evidence for 1 past attack, in the absence of documented objective neurologic findings, can include historical events with symptoms and evolution characteristics for a prior inflammatory demyelinating event; at least 1 attack, however, must be supported by objective findings.

[c]No additional tests are required. However, it is desirable that any diagnosis of MS be made with access to imaging based on these criteria. If imaging or other tests (for instance, CSF) are undertaken and are negative, extreme caution needs to be taken before making a diagnosis of MS, and alternative diagnoses must be considered. There must be no better explanation for the clinical presentation, and objective evidence must be present to support a diagnosis of MS.

[d]Gadolinium-enhancing lesions are not required; symptomatic lesions are excluded from consideration in subjects with brainstem or spinal cord syndromes.

Source: [95] *Table 4*

CONDITIONS THAT MAY MIMIC MS		
Disease	**Symptoms Similar to MS**	**Differentiating Symptoms**
Systemic lupus erythematous	Common in young women and may affect the nervous system, especially the optic nerve and spinal cord. MRI white-matter changes are common, and up to 60% have oligoclonal bands and IgG abnormalities in CSF.	Positive serology with ANA and double-stranded DNA autoantibodies. Systemic involvement, especially including the kidneys and skin, and hematologic changes.
Sjögren syndrome	Occasional reports of neurologic symptoms, especially progressive myelopathy. MRI may show white-matter lesions and CSF may show oligoclonal bands with increased IgG.	Positive serology for SS-A (Ro) and SS-B (La) autoantibodies. Prominent dry eyes and mouth. Salivary gland biopsy can be definitive.
Lyme disease	Can cause persistent focal neurologic findings and signal abnormalities on MRI scan of the brain.	History of erythema migrans rash. Western blot is the most definitive serology, and CSF will show positive PCR.
Syphilis	Can cause optic neuritis, myelopathy, and other focal neurologic findings.	MRI is usually normal. Negative serology rules out syphilis. Advanced infection now rare except in HIV-positive or immunocompromised patients.
HIV/AIDS	May cause optic neuritis, myelopathy, mental status changes, and focal deficits with white-matter changes on MRI scan and abnormal CSF.	Occurs in high-risk populations who may have diminished CD4 cell counts and positive HIV serology.
Vitamin B12 deficiency	May cause CNS deficits, especially a progressive myelopathy, rarely with MRI signal abnormalities.	Complete blood count is often abnormal and serum B12 levels are low. Methylmalonic acid and homocysteine are often abnormal.
CNS lymphoma	Focal neurologic deficits with multifocal enhancing MRI lesions.	CSF does not have IgG abnormalities but will often show positive cytology. Lesions are highly steroid responsive. Brain biopsy may be necessary.
Chiari malformation	May cause cranial neuropathies, including ophthalmoplegia, nystagmus, and ataxia.	MRI scanning, especially on sagittal images, will detect the malformation. MRI of the brain is otherwise normal, as is CSF.
Chronic fatigue syndrome and fibromyalgia	May report neurologic symptoms that mimic MS in a similar population (young women).	Neurologic examination is objectively normal. Difficulties arise when the MRI shows "nonspecific" abnormalities, but MRI, CSF, and VERs should be normal.
ANA = antinuclear antibody, CSF = cerebral spinal fluid, HIV/AIDS = human immunodeficiency virus/acquired immunodeficiency syndrome, MRI = magnetic resonance imaging, PCR = polymerase chain reaction, VER = visual evoked response.		
Source: [96]		*Table 5*

clinically isolated syndrome and fulfillment of clinical or MRI criteria for dissemination in space with demonstration of CSF-specific oligoclonal bands in the absence of other CSF findings. In addition, symptomatic and asymptomatic MRI lesions can be considered in the determination of dissemination in space or dissemination in time. Previously, only asymptomatic MRI lesions could fulfill these criteria. Finally, cortical lesions (in addition to juxtacortical lesions) can be used in fulfilling MRI criteria for dissemination in space [95].

DIFFERENTIAL DIAGNOSIS

Because there are a variety of conditions that may mimic MS, differential diagnosis can be complicated (***Table 5***) [96]. A diagnosis of MS should be questioned if clinical or laboratory findings are unexpected or atypical. These unusual features, or "red flags," should raise suspicion that another condition is the underlying cause of symptoms.

Atypical clinical features that suggest an alternate diagnosis include [96]:

- Normal neurologic examination
- Abnormality in a single location (i.e., no dissemination in space)
- Progressive from onset (i.e., no dissemination in time)
- Onset in childhood or at an age older than 50 years
- Psychiatric disease present
- Systemic disease present
- Prominent family history (may suggest genetic disease)

- Gray matter symptoms (e.g., dementia, seizures, aphasia)
- Peripheral symptoms (e.g., peripheral neuropathy, fasciculations)
- Acute hemiparesis
- Lack of typical symptoms (e.g., no optic neuritis, bladder problems, Lhermitte sign)
- Prolonged benign course (i.e., diagnosis made several years ago with few current findings)

Atypical laboratory findings that point to a diagnosis other than MS as the cause of symptoms include [96]:

- Normal or atypical MRI
- Normal CSF
- Abnormal blood tests (though false positives are possible)

Most patients with other diseases will be identified by the presence of one or more of these atypical features. A number of studies have demonstrated that patients who do not have MS have two things in common: absence of typical MS symptoms such as optic neuritis, Lhermitte sign, sensory dysfunction, neurogenic bladder, or other common deficits; and absence of typical findings on MRI and CSF examination [96]. Very few patients with MS have a normal brain MRI and/or normal CSF.

EVIDENCE-BASED PRACTICE RECOMMENDATION

In the absence of a clear-cut typical clinically isolated syndrome, the International Panel on Diagnosis of Multiple Sclerosis asserts that caution should be exercised in making the diagnosis of multiple sclerosis, and the diagnosis should be confirmed by further clinical and radiological follow-up. In such cases, the clinician should consider postponing making a definitive diagnosis and initiation of long-term disease-modifying therapies, pending longer follow-up to accumulate additional evidence supporting the diagnosis.

(https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(17)30470-2/fulltext. Last accessed December 12, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

Misdiagnosis of MS

Although uncommon, a misdiagnosis of MS can result in unnecessary and prolonged therapies that impose potentially harmful risks to patients. In a multi-center study of 110 misdiagnosed patients, alternate diagnoses included migraine (22%), fibromyalgia (15%), nonspecific or nonlocalizing neurologic symptoms with abnormal MRI (12%), conversion or psychogenic disorders (11%), and neuromyelitis optica spectrum disorder (6%) [97]. The duration of misdiagnosis was 10 years or longer in one-third of patients. Seventy-seven patients (70%) had received disease-modifying therapy and 34 (31%) experienced unnecessary morbidity because of the misdiagnosis. The most common errors in diagnosis pertained to misinterpretation of MRI findings or misapplication of clinical and radiographic criteria for the diagnosis of MS.

TREATMENT

There is no cure for MS. However, effective treatment strategies are available to modify the disease course, treat or reduce exacerbations, prevent relapses, manage signs and symptoms, improve overall function and safety, and provide psychological support. The treatment strategy depends on the patient's clinical condition and disease course. In cases of mild MS without relapses, usually no treatment is necessary. If a patient experiences relapses or if symptoms become more severe, treatment should be initiated as soon as possible.

TREATMENT OF ACUTE EXACERBATIONS

Treatment of the acute exacerbations seen with relapsing types of MS relies primarily on corticosteroids and adrenocorticotropic hormone (ACTH). These agents have been found to promote speedier resolution of the neurologic deficits, lessen the severity of an attack, and effectively reduce the risk of permanent residual deficits. Both corticosteroids and ACTH are capable of restoring the breakdown of the blood-brain barrier, reducing inflammation, and immunomodulating mononuclear trafficking mechanisms. Corticosteroids also promote quick recovery from disability [98; 99].

Corticosteroid therapy is indicated for patients with MS who present with an acute exacerbation (relapse) accompanied by objective evidence of functional neurologic impairment, such as impairment of vision, signs of optic neuritis, motor deficits or cerebellar symptoms and signs, or sensory deficits that impose undue discomfort (e.g. paresthesias).

The first-line treatment of MS-related exacerbations involves administration of high doses of IV corticosteroids, usually methylprednisolone (1 g daily), for five to seven days [100; 101]. Alternative approaches for patients who do not tolerate large intravenous dosage or have poor venous access include:

- Repository ACTH (corticotropin injection gel): 80–120 units daily for one to three weeks
- Oral prednisone: 500–1,250 mg daily divided for three to seven days
- "Smoothie Medrol:" 1 g methylprednisolone mixed in smoothie or juice taken orally with breakfast for three to seven days
- Dexamethasone: 160–200 mg orally/IV daily divided for three to seven days

Although frequently used, the evidence to support low-dose oral prednisone in the treatment of acute relapses is poor and is therefore not recommended [102].

An evidence-based assessment of the use of ACTH and corticosteroids in the treatment of MS was undertaken by the Therapeutics and Technology Assessment Committee of the American Academy of Neurology. The Committee concluded that [99]:

- Treatment with corticosteroids promotes quicker recovery from acute attacks of MS.
- Long-term benefits of corticosteroids and ACTH on the course of MS are yet to be seen.
- Although high-dose corticosteroids are used to treat acute exacerbations, there is no compelling evidence that using one specific type of agent, route of administration, or dose is more beneficial than another.

Potential side effects of corticosteroids include osteoporosis, changes in mood, and memory defects [103; 104]. Patients treated with oral corticosteroids also may experience alterations in blood glucose, glaucoma, gastrointestinal symptoms, and psychiatric disorders [105].

Patients on interferons or glatiramer acetate can receive the initial pulse of corticosteroids or ACTH with or without subsequent tapering of the corticosteroid dose. Patients taking natalizumab should limit corticosteroids to a shorter duration (i.e., two to three days) without a taper to avoid the risk of developing an opportunistic infection, such as progressive multifocal leukoencephalopathy [99]. An oral steroid taper is not generally recommended. However, if there has been a dramatic response to IV corticosteroids (the so-called "Lazarus" effect), then a short taper may prevent rebound edema and a consequent deterioration [102].

IV immunoglobulins (0.4 g/kg/day for five days) are also used in some cases to treat MS relapse in patients who are intolerant or refractory to steroid treatment (second- or third-line) [106]. However, clinical studies have not resulted in conclusive supporting evidence for its efficacy.

Several other drugs that suppress the immune system (e.g., cyclophosphamide, methotrexate, azathioprine, cladribine, cyclosporine) can also reduce the symptoms of MS. These agents suppress the number of circulating immune cells, which in turn slows the autoimmune process and prevents neural damage. However, use of immunosuppressive agents results in increased susceptibility to various types of infection, and the long-term use of these medications may result in additional side effects.

PLASMAPHERESIS

It is now known that B-cell immunity also plays a key role in the pathogenesis of MS. Plasma exchange may be beneficial for relapsing forms of MS in which severe neurologic exacerbations prove refractory to parenteral corticosteroid therapy. It may also be beneficial for some patients with severe, rapidly progressive MS and similar disorders; however, it does not show any efficacy for SPMS or PPMS.

According to the American Academy of Neurology, plasmapheresis as adjunctive therapy is probably effective for the management of exacerbations in relapsing forms of MS, based on a single class I study.

(https://www.aan.com/PressRoom/Home/GetDigitalAsset/8468. Last accessed December 12, 2022.)

Level of Evidence: Class I (Randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population)

A randomized, sham-controlled study of plasma exchange was conducted in 28 patients with recently acquired severe neurologic deficits resulting from acute inflammatory demyelinating diseases (43% with MS) [107]. Treatment consisted of plasma exchange every 2 days for 14 days. Moderate or greater improvement in neurologic disability was observed during 8 of 19 (42%) courses of active plasma exchange treatment compared with 1 of 17 (6%) courses of sham treatment. Improvement occurred early in treatment and, with the exception of four patients, was sustained over six months follow-up [107].

Plasmapheresis is indicated for patients with severe relapses who have failed to respond to IV corticosteroids. Treatment effects can be dramatic. Research has linked treatment response to type II pathology (i.e., IgG deposition and complement activation) [102].

DISEASE-MODIFYING THERAPY

The use of disease-modifying drugs has been shown to reduce the number of clinical and subclinical attacks and delay the progression of disease in patients with RRMS (***Table 6***) [108; 109; 110]. Early successful control of disease activity is important in preventing the accumulation of disability and protecting quality of life. At present, there are more than one dozen therapeutic agents approved by the U.S. Food and Drug Administration (FDA) for treatment of relapsing forms of MS. This includes five preparations of interferon beta and a growing number of monoclonal antibodies. The exact mechanism of action of these drugs is still not clear, but it is believed to be the result of immunomodulation regulating the activation of impaired immune cells. Additionally, the blood-brain barrier becomes less permeable with immunomodulation, allowing fewer immune cells to enter the brain and reducing the autoimmune reaction between the immune cells and neuronal tissue. All medications differ in their efficacy, and additional data related to their long-term effects are necessary [111; 112; 113; 114; 115].

APPROVED LONG-TERM TREATMENTS FOR MS				
Drug	**Type**	**Side Effects**	**Administration**	**Notes**
Self-injected medications				
ß-interferon 1a[a] (Avonex)	Immunomodulator with antiviral properties	Flu-like symptoms, headache	30 mcg IM injection weekly	Side effects may be prevented and/or managed effectively through various treatment strategies; side effect problems are usually temporary. Blood tests may be given periodically to monitor liver enzymes, blood-cell counts, and neutralizing antibodies.
ß-interferon 1b[a] (Betaseron, Extavia)	Immunomodulator with antiviral properties	Flu-like symptoms, injection-site skin reaction, blood count and liver test abnormalities	250 mcg SC injection every other day	Side effects may be prevented and/or managed effectively through various treatment strategies; side effect problems are usually temporary. Blood tests may be given periodically to monitor liver enzymes, blood-cell counts, and neutralizing antibodies.
Glatiramer acetate (Copaxone, Glatopa, generic)	Immunomodulator that inhibits attacks on myelin	Injection-site skin reaction as well as an occasional systemic reaction—occurring at least once in approximately 10% of those tested	20 mg SC injection daily or 40 mg SC injection three times per week	Systemic reactions such as flushing, dizziness, anxiety, and chest tightness arise 5 to 15 minutes following injection. The symptoms persist for a few minutes and lack long-term adverse effects; specific treatment is unnecessary.
ß-interferon 1a[a] (Plegridy)	Immunomodulator with antiviral properties	Flu-like symptoms, injection-site reaction, blood count and liver test abnormalities	125 mcg SC injection once every two weeks	Side effects may be prevented and/or managed effectively through various treatment strategies; side effect problems are usually temporary. Blood tests may be given periodically to monitor liver enzymes, blood-cell counts, and neutralizing antibodies.
ß-interferon 1a[a] (Rebif)	Immunomodulator with antiviral properties	Flu-like symptoms, injection-site skin reaction, blood count and liver test abnormalities	44 mcg SC injection three times per week	Side effects may be prevented and/or managed effectively through various treatment strategies; side effect problems are usually temporary. Blood tests may be given periodically to monitor liver enzymes, blood-cell counts, and neutralizing antibodies.
Ofatumumab (Kesimpta)	Monoclonal antibody that binds to and depletes B cells associated with MS disease activity	Upper respiratory tract infection, headache	20-mg dose monthly self-administered SC	Serious side effects include infections, HBV reactivation, PML, weakened immune system, injection-related reactions.
Infused medications				
Alemtuzumab (Lemtrada)	Humanized monoclonal antibody that rapidly depletes or suppresses immune system cells (T and B cells), which can damage the myelin and nerves of the CNS	Rash, itching, headache, pyrexia, nasopharyngitis, nausea, diarrhea and vomiting, insomnia, numbness/tingling, dizziness, pain, flushing, infection	Five-day course of IV infusion followed one year later by a second three-day course	Adverse events can include infusion reactions, an increased risk of infection, emergent autoimmune diseases, immune thrombocytopenic purpura (ITP), and an increased risk of malignancies including thyroid cancer, melanoma and lymphoproliferative disorders. For early detection and management of these risks, the drug is only available through a restricted distribution program.

Table 6 continues on next page.

APPROVED LONG-TERM TREATMENTS FOR MS *(Continued)*				
Drug	**Type**	**Side Effects**	**Administration**	**Notes**
Infused medications (Continued)				
Mitoxantrone (Novantrone)	Antineoplastic immunomodulator/ immunosuppressor	Usually well tolerated; side effects include nausea, thinning hair, amenorrhea, bladder infection, and mouth sores. Additionally, urine and whites of the eyes may turn a bluish color temporarily.	IV infusion once every three months (for two to three years maximum)	Carries the risk of cardiotoxicity and leukemia; it may not be given beyond two or three years. People undergoing treatment must have regular testing for cardiotoxicity, white blood cell counts, and liver function. Because of the potential risks, it is seldom prescribed for MS. Anyone who is taking or has taken mitoxantrone should have annual evaluations of his or her heart function, even if no longer receiving this medication.
Ocrelizumab (Ocrevus)	Humanized monoclonal antibody designed to selectively target CD20-positive B cells	Infusion reactions, increase in infections, most commonly upper respiratory tract in patients with RMS and PPMS or skin and lower respiratory tract infection in patients with PPMS	600 mg IV every six months. For the initial dose, two 300-mg doses are given, separated by two weeks.	Should not be used in patients with hepatitis B infection or a history of life-threatening infusion-related reactions to the drug. Other rare adverse events, including cancer and progressive multifocal leukoencephalopathy (PML), could potentially occur, but these risks are still being studied.
Natalizumab (Tysabri)	Humanized monoclonal antibody	Headache, fatigue, depression, joint pain, abdominal discomfort, infection	IV infusion every four weeks	Risk of infection (including pneumonia) was the most common serious adverse event (occurring in a small percentage of patients). The TOUCH Prescribing Program monitors patients for signs of PML, an often-fatal viral infection of the brain. Risk factors for PML include the presence of JC virus antibodies, previous treatment with immunosuppressive drugs, and taking natalizumab for more than two years.
Oral medications				
Teriflunomide (Aubagio)	Immunomodulator affecting the production of T and B cells	Headache, elevations in liver enzymes, hair thinning, diarrhea, nausea, neutropenia, paresthesia	7 mg or 14 mg tablet once daily	More severe adverse events include the risk of severe liver injury and the risk of birth defects if used during pregnancy. A TB test and blood tests for liver function must be performed within six months prior to initiation of therapy, and liver function must be checked regularly. If liver damage is detected, or if a patient becomes pregnant while taking this drug, accelerated elimination is prescribed.

Table 6 continues on next page.

APPROVED LONG-TERM TREATMENTS FOR MS *(Continued)*				
Drug	**Type**	**Side Effects**	**Administration**	**Notes**
Oral medications (Continued)				
Fingolimod (Gilenya)	S1P-receptor modulator	Headache, flu, diarrhea, back pain, abnormal liver tests, cough	0.5 mg capsule once daily	Other adverse events include a reduction in heart rate (dose-related and transient); infrequent transient AV conduction block of the heart; a mild increase in blood pressure; macular edema; reversible elevation of liver enzymes; and a slight increase in lung infections (primarily bronchitis). Infections, including herpes infection, are also of concern. A six-hour observation period is required immediately after the first dose to monitor for cardiovascular changes.
Cladribine (Mavenclad)	Selectively targets and depletes the immune system's B cells and T cells, followed by a "reconstitution," as new B cells and T cells are produced	Upper respiratory tract infections, headache, and decreased lymphocyte counts	Two annual courses of up to 20 days over two years. No treatment is needed for years 3 and 4.	Potential adverse events include lymphopenia and herpes zoster infection. Increased risk of malignancy and fetal harm. Should not be used in patients with an increased risk of cancer or who are pregnant; men and women of reproductive potential must use effective contraception.
Siponimod (Mayzent)	Primary actions at the S1P1 and S1P5 receptors, blocking movement of lymph cells from lymph nodes	Headache, hypertension, changes in liver function tests	After starting at a low dose, the recommended maintenance dosage is 2 mg taken orally once daily starting on day 6	Serious adverse events include a decrease in white blood cells, heart rate, and rhythm abnormalities, as well as hypertension, swelling of the macula of the eye, varicella zoster reactivation, and convulsions. Patients should be monitored for changes in vision caused by macular edema, transient decreases in heart rate, decline in lung function, and changes in liver enzymes. Women who could become pregnant should use contraception to avoid potential risk of fetal harm.
Dimethyl fumarate (Tecfidera)	Immunomodulator with anti-inflammatory properties	Flushing and gastrointestinal events, reduced lymphocyte counts, elevated liver enzymes (rare)	240 mg tablet twice daily	Other possible adverse events include mild or moderate upper respiratory infection, pruritus, and erythema. In studies, the only serious adverse events to occur in two or more patients were gastroenteritis and gastritis. Reduced lymphocyte counts were seen during the first year of treatment. Liver enzymes were elevated in 6%, compared to 3% on placebo.
Monomethyl fumarate (Bafiertam)	Immunomodulator with anti-inflammatory properties	Flushing, gastrointestinal events, redness, itching, rash, diarrhea	Starting dose one 95-mg tablet twice daily for 7 days. Maintenance two 95-mg tablets (total 190 mg) twice daily.	Side effects similar to those listed for dimethyl fumarate, including allergic reactions, PML, serious infections, and liver injury.

Table 6 continues on next page.

APPROVED LONG-TERM TREATMENTS FOR MS *(Continued)*				
Ponesimod (Ponvory)	S1P-receptor modulator	Upper respiratory tract infections, elevated liver enzymes, hypertension	Using a 14-day starter pack, the dose starts low and gradually increases to 20 mg taken orally, once per day.	Adverse effects can include more serious infections and a slowed heartrate (bradycardia or bradyarrhythmia). Contraindicated in those with certain heart conditions, or women who are planning to be or are currently pregnant.
Diroximel fumarate (Vumerity)	Immunomodulator with anti-inflammatory properties	Flushing, stomach problems	231 mg twice daily	The exact mechanism of action by which this medication exerts therapeutic effect in MS is not completely understood. However, upon entering the body, the medication is rapidly converted into the molecule monomethyl fumarate, which is the same active component found in dimethyl fumarate.
Ozanimod (Zeposia)	S1P-receptor modulator	Upper respiratory infection, elevated liver enzymes, orthostatic hypotension	0.92 mg once daily	This medication is started at a lower dose and gradually increased until the full dose is reached, reducing the risk of a transient decrease in heartrate and atrioventricular conduction delays, which may occur if introduced too quickly. Warnings include an increased risk of infections, heart rhythm issues, liver injury, fetal risk, a decline in pulmonary (respiratory) function, and macular edema (swelling behind the eye).

[a]Additional information about interferons: Some individuals develop neutralizing antibodies to the interferons, but their impact on the effectiveness of these medications has not been established. Many continue to do well on these drugs despite the presence of neutralizing antibodies. Others may have sub-optimal results even without neutralizing antibodies present. The MS Council and the American Academy of Neurology have concluded that the higher-dosed interferons are likely to be more effective than lower-dosed interferons. Several factors, however, must be considered when selecting one of these drugs, and this decision must be made on an individual basis.

AV = atrioventricular, IM = intramuscular, IV = intravenous, JC = John Cunningham virus, PML = progressive multifocal leukoencephalopathy, SC = subcutaneous, TB = tuberculosis.

Source: Reprinted with permission from Multiple Sclerosis Association of America. Long-Term Treatments for Multiple Sclerosis. Available at https://mymsaa.org/ms-information/treatments/long-term. *Table 6*

In 2018, the American Academy of Neurology published its practice guideline *Disease-Modifying Therapies for Adults with Multiple Sclerosis*, providing evidence-based recommendations for initiating treatment, switching therapies, and discontinuing disease-modifying agents. The full guideline is available at https://www.aan.com/Guidelines/home/GuidelineDetail/898.

Initiation of treatment with an FDA-approved disease-modifying agent is indicated upon diagnosis of relapsing MS, regardless of the patient's age. For the patient with a first clinical event (clinically isolated syndrome) who meets the revised McDonald diagnostic criteria for MS, disease-modifying therapy should be offered and the option of initiating treatment versus expectant management (awaiting a second clinical event) should be thoroughly discussed. Once initiated, disease-modifying treatment is continued indefinitely unless there is a suboptimal therapeutic response, intolerable side effects, or unsatisfactory adherence to the regimen.

According to the American Academy of Neurology, clinicians must screen for certain infections (e.g., hepatitis, tuberculosis, varicella zoster) according to prescribing information before initiating the specific immunosuppressive or immunomodulating medication planned for use and should treat patients testing positive for latent infections before MS treatment according to individual prescribing information.

(https://n.neurology.org/content/93/13/584. Last accessed December 12, 2022.)

Strength of Recommendation: A (Must be offered) and B (Should be offered)

ß-Interferons

The main disease-modifying drugs used in the treatment of MS are ß-interferons. These are naturally occurring immunomodulating agents that inhibit inflammatory reactions and limit cytokine secretion and lymphocyte migration. Two types of ß-interferon are available: ß-interferon 1a and ß-interferon 1b. ß-interferon 1a is produced by mammalian cells, while ß-interferon 1b is produced in modified Escherichia coli. The mechanisms of these two types are similar, but the dosage and method/frequency of administration may vary.

The use of ß-interferon reduces the risk and severity of clinical exacerbations of MS by about 30%, reduces the risk of developing new MRI lesions by 70% to 90%, and improves the integrity of the blood-brain barrier [99]. As such, it has been shown to slow disease progression and positively impact physical, emotional, and intellectual capacities.

The potential side effects of the interferons include flu-like symptoms and headache. Arthralgias may occur but can be reduced significantly by starting nonsteroidal anti-inflammatory drugs (NSAIDs) before the treatment. Patients treated with interferon should be monitored with periodic laboratory tests to check for liver dysfunction, anemia, leukopenia, and thyroid dysfunction. These studies should be performed at baseline, at three months after initiating the interferon therapy, and every six months thereafter [99]. Skin breakdown at the injection site is also possible.

Approximately 30% of patients with MS do not respond to treatment with a ß-interferon [116; 117]. For these individuals, other pharmacotherapies are available.

Glatiramer Acetate

Another disease-modifying drug approved for the treatment of RRMS is glatiramer acetate (also known as copolymer-1). Glatiramer is believed to block myelin-damaging T-cells, although its exact mechanism of action is not clearly understood. It is a potent immunomodulator that increases the number of immune regulatory cells. These cells reduce inflammation by suppressing the immune response.

Glatiramer acetate reduces the risk and severity of MS attacks and reduces MRI lesions over time. Studies comparing treatment with ß-interferon 1b or glatiramer have demonstrated similar efficacy. Glatiramer acetate has fewer adverse effects compared to the ß-interferons. Good injection technique and site rotation can help to reduce post-injection site reactions, but in some cases, repetitive injection of glatiramer acetate can cause lipoatrophy [118].

Mitoxantrone

Mitoxantrone, a cytostatic drug and a powerful anti-inflammatory, is used in the treatment of both RRMS and progressive forms of MS [119; 120]. It is considered one of the most effective drugs in resolving relapses; however, due to the risks for leukemia and cardiotoxicity, it should only be prescribed to patients with rapidly advancing disease who are refractory to other therapies [121]. Some patients, especially with a subtype of RRMS called rapidly worsening MS, do not respond to immunomodulators and are managed with immunosuppressants, particularly mitoxantrone [122; 123].

Mitoxantrone promotes quick resolution of relapses due to larger lesions in the brain and spinal cord. Various studies have demonstrated a positive effect in people with relapsing-remitting, secondary progressive, and progressive-relapsing subtypes of MS, but it is most beneficial in secondary progressive subtype [124]. Mitoxantrone is discontinued as soon as remission is achieved and replaced with another disease-modifying agent with a better safety profile.

Mitoxantrone causes reduced contraction of cardiac muscles, which can be confirmed by a reduction in ejection fraction measured through multiple gated acquisition scan. Studies have shown that patients receiving doses greater than 140 mg/m^2 have an increased risk of vacuolar cardiomyopathy. As such, it is contraindicated in patients with an estimated ejection fraction less than 50% or a 10% to 15% interval reduction of the ejection fraction [118].

Natalizumab

Natalizumab, a monoclonal antibody, may be used in the treatment of RRMS, and it is considered one of the most effective drugs in reducing the relapse rate (although long-term studies are lacking) [125; 126; 127]. Natalizumab prevents migration of autoreactive lymphocytes into the brain, which results in a profound decrease in CNS mononuclear cell trafficking that reduces MS exacerbations by 70% and disease progression by about 50% [128]. It also accelerates repair of myelin sheath lesions. Some studies have demonstrated that natalizumab can reduce new gadolinium-enhancing lesions by more than 90% [128; 129].

Natalizumab should be prescribed to patients with active RRMS that is refractory or resistant to ß-interferons and glatiramer or patients who cannot tolerate these medications [130]. Natalizumab may be indicated as a first-line treatment in patients with very active disease or in individuals with poor prognosis (e.g., MS targeting the brainstem, cerebellum, and/or spinal cord motor tracks). Studies have demonstrated that a combination of natalizumab with ß-interferon 1a reduces relapses and disability progression more than ß-interferon 1a alone [131]. A biosimilar to natalizumab (natalizumab-sztn) was approved in 2023 and may be considered for any patients with relapsing forms of MS [275].

Several potential side effects are associated with natalizumab. Approximately 1% of patients treated with natalizumab suffer from infusion-related hypersensitivity. This reaction usually occurs at the time of the second dose in natalizumab-naïve patients and can result in the development of a natalizumab-

neutralizing antibody that can reduce the bioavailability of the agent and even render the drug useless. Natalizumab is also associated with an increased risk of developing progressive multifocal leukoencephalopathy. This disorder is caused by the John Cunningham virus, a type of human polyomavirus that infects oligodendrocytes and causes rapid and potentially life-threatening demyelination.

Ocrelizumab

Ocrelizumab is a humanized monoclonal antibody that binds to CD20, a cell surface antigen found on mature B-lymphocytes but not on precursors or plasma cells. Ocrelizumab selectively depletes CD20-expressing B cells. For treatment of MS, the dose is 600 mg by IV infusion every six months. Side effects include infusion reactions, opportunistic infection, and possibly an increased risk of malignancy. In a comparison study against placebo and interferon beta, ocrelizumab achieved a 46% relative reduction in the annualized relapse rate and a 95% reduction in the number of T1 lesions per MRI scan [132]. Ocrelizumab is the only FDA-approved disease-modifying therapy for patients with the PPMS subtype, based on a randomized, placebo-controlled clinical trial that showed lower rates of clinical and MRI disease progression in the treatment arm [133].

Ofatumumab (Kesimpta) received FDA approval in 2020 for adults with relapsing forms of MS, including clinically isolated syndrome, RRMS, and active secondary progressive disease [115; 118]. Ofatumumab is the first self-administered B-cell therapy for MS. It is dosed at 20 mg once weekly for three doses (weeks 0, 1, and 2), with a maintenance dose of 20 mg per month beginning at week 4 [118]. Results of the ASCLEPIOS I and II studies found that ofatumumab demonstrated significant reduction in annualized relapse rate compared with oral teriflunomide. Ofatumumab additionally significantly reduced the mean number of T1 lesions and new or enlarging T2 lesions. A separate post hoc analysis demonstrated that ofatumumab also reduced new disease activity in patients with relapsing forms of MS [134].

Fingolimod

Treatment with fingolimod, a sphingosine-1-phosphate (S1P) receptor modulator, results in reduction of the relapse rate in patients with RRMS; however, it is associated with an increased risk of opportunistic infections, which can be fatal [135; 136; 137; 138]. Fingolimod was the first oral agent with a labeled indication for relapsing forms of MS [136]. It promotes the redistribution of lymphocytes from the circulation to the lymphoid organs and prevents the entry of lymphocytes back into circulation. Several studies have demonstrated that it significantly reduces both clinical and radiographic MS disease activity. Its side effects include first-dose bradycardia, arrhythmia, reactive airway events, macular edema, skin cancers, and increased susceptibility to infections [118]. Fingolimod is the only drug approved for the treatment of highly active (or rapidly worsening) RRMS.

The American Academy of Neurology recommends that clinicians prescribe alemtuzumab, fingolimod, or natalizumab for people with highly active MS.

(https://n.neurology.org/content/90/17/777. Last accessed December 12, 2022.)

Strength of Recommendation: B (Should be offered)

Ozanimod

Ozanimod (Zeposia), another S1P receptor modulator, received FDA approval in 2020 for the treatment of relapsing forms of MS, including clinically isolated syndrome, RRMS, and active secondary progressive disease [139]. Ozanimod blocks the lymphocytes' ability to emerge from lymph nodes, thereby decreasing the amount of lymphocytes available to the CNS and intestine [118]. Unlike earlier drugs of its class, ozanimod is the only FDA approved S1P receptor modulator that does not require genetic testing or first-dose observation [140].

Ponesimod

Ponesimod (Ponvory) received FDA approval in 2021 for treatment of relapsing forms of MS [115]. This S1P receptor modulator is administered orally once per day, beginning at 2 mg and gradually increasing to 20 mg daily [118].

Dimethyl Fumarate

In 2013, dimethyl fumarate (BG-12, Tecfidera) was approved for the initial treatment of relapsing forms of MS [141]. It has not been evaluated in either SPMS or PPMS, so it is generally not recommended in patients without evidence of active inflammation. This agent acts through modulation of oxidative pathways to decrease autoimmunity. Clinical trials indicated a 69% reduction in contrast-enhancing lesions (phase II trial), a 53% reduction in annualized relapse rate, a 38% reduction in disability progression, and a 49% reduction in disability progression after two years [141]. Dimethyl fumarate is taken orally at a dose of 120–240 mg twice daily [141]. Possible side effects include elevated liver enzymes, nausea, diarrhea, flushing, and cramps.

Teriflunomide

Teriflunomide, an active metabolite of the antirheumatic drug leflunomide, is approved for the treatment of RRMS [142]. It has been shown to inhibit cell division in certain immune cells. Results from a phase III trial showed a significantly reduced annualized relapse rate compared to placebo. The risk of disability progression was reduced by 30% for the 14-mg dose and by 24% for the 7-mg dose. Common side effects include headache, nausea, diarrhea, and hair thinning. Use has been associated with rare reports of hepatotoxicity, hepatic failure, and death [118]. Treatment with teriflunomide should not be initiated in patients with pre-existing acute or chronic liver

disease, and use is contraindicated in patients with severe hepatic impairment.

Cladribine

Cladribine is a purine analog approved for the treatment of relapsing forms of MS [143]. In a clinical trial in 1,326 patients with relapsing forms of MS who had at least one relapse in the previous 12 months, cladribine significantly decreased the number of relapses and the progression of disability compared with placebo. The usual oral dose is 3.5 mg/kg over a two-year treatment course [143].

However, the drug includes boxed warnings for malignancy and fetal harm, and other possible adverse effects include hematologic toxicity, bone marrow suppression, and decreased lymphocyte counts. Because of its safety profile, the use of cladribine is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for the treatment of MS [143].

Immunoablation and Stem-Cell Transplantation

Limited studies over the past decade have shown that immunoablation and autologous hematopoietic stem-cell transplantation (AHSCT) can be a highly effective and relatively safe form of therapy in select patients with severe MS. The efficacy of AHSCT relies on achieving profound suppression of inflammatory MS activity, followed by reconstitution of the immune system that confers long-lasting disease remission without need for additional disease-modifying agents. Candidates for this approach are young patients with aggressive inflammatory RRMS refractory to usual treatment. Complete suppression of MS disease activity for four to five years has been documented in 70% to 80% of patients who have undergone AHCST, with a disease-associated mortality of 0.3% [144].

AHSCT is occurring more frequently, with a better safety profile. One review assessed studies from January 2016 to November 2020 that included 20 or more patients [145]. The authors assessed benefits of AHSCT, including no evidence of disease activity, functional and patient-reported outcomes, novel biomarkers (e.g., brain atrophy), and cost-effectiveness of the treatment. The overall efficacy of AHSCT was found to be better than standard treatments. Younger patients with highly active disease had a greater chance for improvement. Patients with comorbidities and more failed treatments who are in a more progressive disease phase may not respond as well to AHSCT. Results from currently enrolling randomized controlled trials, as well as ongoing registries, will provide more evidence for the safe and appropriate use of AHSCT [145].

SYMPTOM MANAGEMENT

The primary goal of symptomatic MS therapy is to improve quality of life by eliminating or reducing symptoms affecting patients' functional abilities. The approaches to symptomatic treatment focus on controlling the symptom rather than the underlying disease process.

The interventions chosen will depend on the patient's symptoms, medical history, and overall health. A comprehensive approach that incorporates pharmacotherapy, physiotherapy, and psychotherapy is superior to medical management alone.

Fatigue

Approximately 80% of patients with MS experience significant fatigue at some stage of their disease, often to the point of affecting their ability to complete activities of daily living [146]. This fatigue differs from normal exhaustion or tiredness, which usually increases during the day; it may be present at any time, even upon waking, and can limit a patient's professional and social life. MS-associated fatigue is aggravated by increases in body temperature (referred to as Uhthoff phenomenon). Depression can often be masked by symptoms of fatigue, so this is an important differential diagnosis, particularly in early stages of MS.

The Modified Fatigue Impact Scale (MFIS) is commonly used in patients with MS to assess the effects of fatigue in terms of physical, cognitive, and psychosocial functioning. The full-length MFIS consists of 21 items and takes 5 to 10 minutes to administer; the abbreviated version contains five items and can be administered in 2 to 3 minutes. The MFIS is a structured, self-report questionnaire [147]. The MFIS items are divided into three subscales (i.e., physical, cognitive, psychosocial) as well as a total score. All items are scaled so that higher scores indicate a greater impact of fatigue on the patient's activities [148].

There are no licensed therapies for MS-related fatigue, but both amantadine and modafinil are widely prescribed off-label [102]. These drugs and pemoline and L-carnitine have been shown to be effective in improving fatigue severity [149]. However, stimulants should be used with caution—there is little evidence to support their efficacy, and they commonly cause anxiety and insomnia [102]. Physiotherapy, occupational therapy, and lowering body temperature may also help reduce fatigue and improve quality of life. Aminopyridines are effective in the amelioration of Uhthoff phenomenon [38].

Spasticity

More than 80% of patients with MS experience some spasticity, with 30% having symptoms so significant that they modify or eliminate daily activities as a result. Patients should be screened for pain, infection, fever, and bowel distention, as these factors are associated with more severe spasticity.

Spasticity may be classified as:

- Tonic: Muscle tone is constantly elevated.
- Phasic: Muscle tone is intermittently elevated and is usually accompanied by pain.

Classification is usually done using the Modified Ashworth Scale, which measures resistance to passive stretch (***Table 7***) [150; 151]. A higher score is indicative of more severe spastic hypertonia. Clinical assessment of spasticity may also include muscle grading, deep tendon reflexes, and measurements of

MODIFIED ASHWORTH SCALE FOR SPASTIC HYPERTONIA	
Score	**Description**
0	No increase in tone
1	Slight increase in muscle tone, manifested by a catch and release or minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension
1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the range of motion
2	More marked increase in muscle tone through most of the range of motion, but affected part(s) easily moved
3	Considerable increase in muscle tone, passive movement difficult
4	Affected part(s) rigid in flexion or extension

Source: Reprinted from Phys Ther. 1987;67:206-207, with permission of the American Physical Therapy Association.
 Table 7

range of motion. The Modified Ashworth Scale is also useful for evaluating and determining the response to therapy over time.

Treatment of spasticity involves an optimum amalgamation of drug therapy, maintenance and restorative therapies, and assistive devices. In addition to reducing hypertonia, the multidisciplinary approach may include interventions to relieve pain, improve overall motor function, and prevent or treat complications such as pressure ulcers and contractures.

Tonic spasms usually manifest as part of an acute relapse and are self-limiting. They typically respond to low or moderate doses of sodium-channel blockers [102]. However, phasic spasms require more intensive treatments.

Baclofen and tizanidine are commonly used to treat and reduce spasticity, and the benzodiazepines (e.g., diazepam) also have a beneficial effect. Other possible agents include gabapentin and dantrolene [102]. In general, baclofen is considered the drug of choice for spasticity in patients with MS [152]. An intrathecal baclofen pump may be indicated for patients with unilateral or bilateral phasic lower limb spasticity. Dantrolene should be used with caution because of the potential for hepatotoxicity [102].

Injectable forms of botulinum toxin, phenol, or alcohol are especially beneficial in patients with focal spasticity or difficulty tolerating oral medications; however, there is limited evidence for the use of botulinum toxin for the treatment of MS spasticity [153]. Studies are ongoing to determine the safety, efficacy, and potential for such use of botulinum toxin [154; 155; 156]. Surgical intervention (tenotomy) is indicated in severe cases.

Patients should be advised to avoid or minimize exposure to triggers and maintain proper positioning, posture, and ergonomics as much as possible. Stretching exercises are recommended for patients with MS in order to maintain normal muscle tone, especially in the popliteus, gastrocnemius, and lumbricals. Patients with significant lower limb weakness often rely on spasticity to splint their legs for weight bearing and walking [102].

Bladder Dysfunction

Bladder dysfunction is seen in approximately 80% of patients with newly diagnosed MS and in 96% of patients after 10 years [33]. Bladder dysfunction can lead to urgency, detrusor hyperactivity with restricted storage capacity, incontinence, and frequent micturition. A careful history and physical examination should be conducted on these patients, usually involving urinalysis and uroflowmetry (ultrasound) with a postvoid residual. This is especially important because a patient's subjective assessment of his or her bladder function may not correlate with postvoid residual volumes. High postvoid residual volumes (>100 cc) are associated with an increased risk for recurrent infections, calculi, and hydronephrosis. In such cases, the patient should be referred to a neurourologist for further evaluation. A thorough pelvic floor examination is required.

Patients who experience failure-to-store syndrome (also referred to as a "spastic" or "small" bladder) will usually report urgency, frequency, and nocturia. They usually have small bladder volumes and demonstrate a spastic detrusor muscle pattern on urodynamic testing. Failure-to-store may be treated with an antimuscarinic, an anticholinergic, or a mixed agent like oxybutynin [102]. The tricyclic antidepressant imipramine may also be beneficial in such cases.

Patients with the primary problem of failure to empty usually have an outlet disorder, such as an overactive sphincter or a hyporeflexic or areflexic bladder. These patients often suffer from frequency, hesitation, slow stream/dribbling, and prolonged voiding time. Failure-to-empty conditions are generally treated with an alpha-antagonist, such as doxazosin, prazosin, terazosin, or tamsulosin. The highly selective agent silodosin may also produce good results, although its affinity for the prostate can cause erectile dysfunction. Prophylactic antibiotic treatment with nitrofurantoin or sulfamethoxazole/trimethoprim may be indicated in patients with recurrent urinary tract infections.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The National Institute for Health and Clinical Excellence recommends offering bladder wall injection with botulinum toxin type A to adults with MS and symptoms of an overactive bladder in whom antimuscarinic drugs have proved to be ineffective or poorly tolerated.

(https://www.nice.org.uk/guidance/cg148. Last accessed December 12, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

Patients who experience nocturia or nocturnal enuresis should be advised to empty their bladder before going to bed and decrease or avoid fluid intake two to three hours prior bedtime. Caffeinated products, alcoholic beverages, and spicy and acidic foods can cause bladder irritation and urinary frequency and should be avoided. If these behavioral strategies are ineffective, treatment with oral desmopressin is indicated [157].

Sacral neuromodulation may be beneficial for patients with incontinence related to overactive bladder, particularly if it is refractory to other treatments. Patients can be instructed to practice the Valsalva or Credé maneuver to help with hesitancy (in conjunction with pharmacotherapy). Chemical denervation of the detrusor muscle using intravesical capsaicin or botulinum toxin injections may be helpful in some cases [102].

Clean, intermittent or permanent catheterization is used for patients who do not respond to other treatments. A suprapubic catheter is preferred over intraurethral (Foley) because of the lower risk of infection and urethral damage. Surgical options (e.g., augmentation cystoplasty, ileovesicostomy, ileal conduit urinary diversion) should be considered for patients with severely impaired emptying or patients with repeated MS exacerbations triggered by recurrent infections. Other nonpharmacologic options that may be incorporated into the treatment plan include:

- Pelvic floor muscle strength training
- Bladder retraining
- Biofeedback
- Pessaries

Bowel Dysfunction

Bowel dysfunction affects approximately 70% of patients with MS [157]. The majority of patients experience either constipation or fecal incontinence.

Constipation

Clinically, constipation is defined as infrequent bowel movements (fewer than three per week). The etiology of constipation in patients with MS is multifactorial, and a careful assessment of diet and fluid intake is essential. Reduced fluid intake due to bladder disturbances or dysphagia may be a contributing factor. Certain drugs used to treat other symptoms of MS, such as spasticity, pain, or bladder dysfunction, can also result in constipation. Decreased physical activity and mobility can, in turn, reduce the frequency of bowel movements. A screening of secondary medical causes should also be completed.

The first step in addressing mild-to-moderate constipation is to start behavioral changes. This includes increasing physical activity, ensuring appropriate fluid intake (1.5–2 liters per day), and increasing dietary fiber (at least 25–35 g per day) [102]. Biofeedback therapy may also be effective in improving motility.

Osmotic agents, such as magnesium oxide and magnesium sulfate, are often used in the treatment of mild-to-moderate constipation. Compared to magnesium oxide, magnesium sulfate can lead to violent bowel movements with liquid-like consistency, and therefore, it should be avoided in the elderly and those with limited mobility [157]. Prokinetic agents such as lubiprostone increase intestinal fluid secretion and may be used in some cases. In MS, chronic constipation is often due to gastrointestinal hypomotility; therefore, bulk laxatives may exacerbate the problem [102]. A combination of prokinetic and bulk laxatives may be necessary. Lactulose, polyethylene glycol, and sorbitol are helpful for patients with more severe chronic constipation [157].

Enemas or suppository agents can work quickly and efficiently to soften and expel stool. Saline enemas are reported to be the safest approach [157]. Caregivers should be encouraged to monitor the type of enema being used and its frequency in order to prevent electrolyte imbalance. Various commercial enema products are available, and these may be used at home in cases of chronic constipation. Analgesic or antiemetic rectal suppositories help relieve rectal pain or nausea and vomiting in constipated patients with MS.

Stimulant agents such as senna, cascara, and castor oil increase intestinal motility and secretions and are effective in combating constipation. Senna is the preferred agent because of greater tolerability [157]. Docusate sodium, a stool softener, in combination with senna is effective in treating mild-to-moderate constipation in patients with MS. Surgery is indicated in rare cases of refractory constipation and fecal impaction [157].

Fecal Incontinence

Fecal incontinence is defined as the loss of regular control of the bowels, and in patients with MS, it is usually caused by reduced anal squeeze pressures, correlating with duration of disease and disability status. It is experienced by approximately 24% of mildly disabled patients and 66% of those with severe disease [157]. Evaluation of the patient's diet and fluid history is essential to determining possible triggers. The overall goal is to treat the underlying cause of fecal incontinence.

The opioid-receptor agonist loperamide can be prescribed to patients with chronic diarrhea with or without fecal incontinence, but it is not recommended in patients with symptoms of diarrhea and concomitant constipation [157]. Biofeedback training is helpful in strengthening pelvic floor muscles and

improving anal squeeze pressures. Surgical repair (e.g., pelvic floor muscle repair, forming a new external anal sphincter, use of hydraulic rings) is indicated for medically refractory cases.

Cognitive Impairment

Approximately 40% to 70% of patients with MS experience intellectual impairments that progressively increase with disease duration and result in significant disability, decreased quality of life, and inability to maintain employment [157]. The most common cognitive deficits include poor attention and executive functioning, slowed information processing, and reduced memory retrieval. Patients with MS are capable of consolidating new memories; dementia is rare.

Baseline neuropsychological investigations should be performed at the time of an MS diagnosis so future monitoring of cognitive changes is accurate and can guide medical interventions. Cognitive-behavioral therapy, psychotherapy, and counseling are effective interventions; pharmacotherapy may also be indicated. Some studies have found amphetamines to be effective in improving cognitive performance; however, this may be due to reduction in fatigue and mood changes rather than a beneficial effect on cognition [157]. There is emerging evidence that suggests the centrally acting acetylcholinesterases, such as donepezil, improve memory in subjects with memory impairment [102].

Depression

Due to the potentially overwhelming nature of the medical consequences of MS, psychiatric issues are often overlooked and undertreated. However, an estimated 50% of patients with MS have clinical depression, and the suicide rate is higher among persons with MS than the general population [157; 158]. Common signs and symptoms include insomnia, early morning awakening, loss of appetite, anhedonia, loss of concentration, fatigue, short-term memory deficits, and cognitive impairment.

The Beck Depression Inventory (BDI-II) is often used in the diagnosis and evaluation of depression in patients with MS [158]. The BDI-II is a questionnaire that consists of 21 multiple choice questions that allow self-reporting of a multitude of depressive symptoms. It also is used to measure the severity of depression; higher total scores indicate more severe depressive symptoms.

All patients should be reassured that depression is treatable. A sedating tricyclic antidepressant such as amitriptyline or one of the newer selective serotonin reuptake inhibitors (e.g., citalopram) may be effective in the treatment of depression in patients with emotional lability and/or depression [102]. Venlafaxine or bupropion may be prescribed for mood stabilization if lack of energy or loss of concentration is the main presenting symptom [158]. Patients with anxiety may be treated with an anxiolytic, such as lorazepam, alprazolam, or clonazepam [158]. Buspirone is also prescribed in patients with anxiety and is particularly effective for panic attacks. Hypomania and psychosis are rare manifestations of MS and should be managed according to standard psychiatric principles [102].

Cognitive-behavioral therapy is helpful in patients with MS to address depressive symptoms and maintain commitment to the established care plan. Patients who express suicidal ideation or planning should be referred to emergency psychiatric care immediately.

Uhthoff Phenomenon

Approximately 60% to 80% of patients with MS experience Uhthoff phenomenon, which is characterized by reversible and often stereotypic worsening of neurologic symptoms triggered by increased body temperature [38]. Exposure to high temperature, intense exercise, various infections, and stress can all increase core body temperature. Any factors that cause sweating can result in worsening of neurologic symptoms.

Eliminating undue heat exposure, limiting exercise, and avoiding psychosocial stressors while promoting subsequent cooling can reverse the neurologic deficits caused by Uhthoff phenomenon. Simple strategies to cool the body, such as cold showers, ice packs, and regional cooling devices, provide mild-to-moderate benefits [38]. Cooling suits may be helpful in patients with profound heat sensitivity [102]. Although efficacious, use of 4-aminopyridine, a centrally acting potassium-channel blocker, is limited by side effects [102].

Oculomotor Symptoms

Oculomotor symptoms are experienced by approximately 30% to 50% of all patients with MS [159]. Internuclear ophthalmoplegia and nystagmus are the most common oculomotor conditions, although other visual disturbances can develop.

Oculomotor symptoms that emerge in the relapse period should be treated with high-dose IV methylprednisolone [159]. An eye patch is beneficial during the acute phase to avoid diplopia. Patients with pendular nystagmus are usually treated with gabapentin or memantine; baclofen is the drug of choice for treatment of upbeat/downbeat nystagmus [159]. 3, 4-DAP 20 mg is also effective in treating downbeat nystagmus. In internuclear ophthalmoplegia, drug treatment is rarely needed.

Sexual Dysfunction

Sexual dysfunction is a frequent complication of MS, usually in combination with bladder dysfunction. It tends to develop later in the disease course and is more common in men (90%) than women (70%) [45]. Sexual health and activity should be a part of the regular assessment of patients with MS.

Sexual dysfunction can adversely affect patients' self-esteem, quality of life, and spousal relationships. It can be categorized as primary, secondary, or tertiary depending on cause, and each type requires a different therapeutic approach. Primary sexual dysfunction is the direct consequence of the demyelinating lesions formed in the CNS influencing sexual response and sexual feelings. Secondary sexual dysfunction occurs as a result of other MS symptoms (e.g., spasticity) and/or secondary to the side effects of medications used to treat MS. Tertiary sexual dysfunction is the result of psychological, emotional, and/or cultural influences that may adversely affect sexual response and activity.

Type of sexual dysfunction varies. Reduced libido is the most frequent manifestation of primary sexual dysfunction for women with MS. Among ambulatory men with MS, approximately 60% experience erectile dysfunction, 50% report orgasmic dysfunction, and 40% experience reduced libido [160].

Prostaglandin-5 inhibitors (e.g., sildenafil, vardenafil, tadalafil) are used in the treatment of primary sexual dysfunction in men. Penile prostheses, meatal urethral alprostadil suppository, testosterone supplements, vacuum erection devices, and intracavernosal injections of alprostadil may also be helpful [45; 157].

One single-center, open-label study was conducted from 2011 to 2012 for 24 weeks. The study included 45 patients 18 to 65 years of age with relapsing forms of MS who were natalizumab-naïve and who had a suboptimal response to or tolerability issues with other disease-modifying therapies [161]. Enrolled patients received natalizumab 300 mg IV every 28 days and completed the Multiple Sclerosis Intimacy and Sexuality Questionnaire (MSISQ-19), a self-report tool designed to sel-assess how various MS symptoms have interfered with sexual activity or sexual satisfaction over the previous six months. Patients with known sexual dysfunction reported a decrease in these symptoms while on natalizumab therapy, as demonstrated by a reduction on the primary subscale of the MSISQ-19. However, the small sample size was a limiting factor in the interpretation of the results [161].The EROS Clitoral Therapy Device is the only FDA-approved therapy for women experiencing sexual dysfunction, and it is only indicated in cases of impaired sexual response [162]. This device stimulates clitoral engorgement, resulting in significantly improved vaginal/clitoral sensations, lubrication, ability to achieve orgasm, and overall sexual satisfaction [162]. Use of high-frequency wall-power vibrator devices may be recommended for women who have diminished arousal, sensation, and difficulty achieving orgasm. Over-the-counter water-soluble lubrication agents are helpful for women with vaginal dryness and related pain with intercourse.

Tertiary sexual dysfunction is managed with counseling or therapy, either as monotherapy or as adjunctive treatment in combination with pharmacotherapy or devices. The patient should be educated about sexual stimulation techniques and interpersonal communication. Body mapping, a self-exploration technique in which the patient gently touches all parts of the body to identify erogenous stimulation, may be incorporated into the treatment plan.

Dysphagia

Dysphagia for liquids and solids is a relatively common complication of MS. Studies indicate that it is more likely to occur in patients with severe brainstem impairment and more severe disease [163]. The potential risk of aspiration, pneumonia, and malnutrition and the high efficacy of swallowing rehabilitation suggest that patients with MS should have a careful evaluation of swallowing function, especially high-risk patients [163].

Screening for dysphagia, both solid and liquid, is required at each office visit. Individuals with liquid dysphagia usually complain of coughing or choking while eating, whereas those with solid food dysphagia have a sensation of food "sticking" in the throat or chest. Other clinical manifestations include dysphonia, coughing, and gastroesophageal reflux disease.

Patients with dysphagia should undergo a thorough assessment that includes a comprehensive history and examination related to particular symptoms of dysphagia, ear/nose/throat and neurologic examination, and a functional swallowing test. A videofluorographic swallowing study or transnasal fiberoptic endoscopic examination of swallowing is also helpful. A careful physical examination should include inspection and palpation of the neck and throat for structural abnormalities or masses. A videofluoroscopic swallowing study can be performed in the form of a modified barium swallow.

If present, treatment focuses on proper fluid and food intake, prevention of aspiration and secondary pneumonia, and improvements in quality of life using pharmacologic, rehabilitative, and/or surgical interventions. Anticholinergic drugs (e.g., scopolamine) may be prescribed if hypersalivation is an issue; transdermal patches are the preferred administration method. Injections of botulinum toxin can increase esophageal sphincter tone. Proton pump inhibitors are highly effective in controlling symptoms of gastroesophageal reflux.

However, the basis of dysphagia treatment in patients with MS is functional swallowing therapy. This involves restitution (restoration of impaired function using exercises), compensation (postural changes and dietary modifications), and adaptation (modification of the environment to improve nutrition). This therapy is conducted by a speech-language pathologist.

For patients with severe neurogenic dysphagia or hypersecretion, a nasogastric or percutaneous endoscopic gastrostomy tube may be temporarily or permanently required to maintain adequate nutritional and fluid intake. These tubes have been found to lower choking risk and improve quality of life and survival rate in certain patients. A nasogastric tube is indicated when enteral feeding is required for a short duration (i.e., less than 30 days). However, direct enteral access is preferred when enteral feeding is required for a longer period, as nasogastric tubes cause considerable discomfort and epistaxis.

Dysarthria

Dysarthria is a motor speech disorder caused by impairment of the nerves that control the muscles involved with speaking. Approximately 40% of patients with MS experience some level of dysarthria, which is usually heightened during times of stress or fatigue [164].

No drug treatment is effective for the treatment of dysarthria, but speech therapy can be very beneficial in improving voice volume and language. Speech-language pathologists can also recommend the use of voice amplifiers to aid communication.

Pain

Acute, intermittent bouts of pain may occur in association with optic neuritis, trigeminal neuralgia, dysesthesias, or Lhermitte sign, and treatment is dependent on the causative condition [165]. Corticosteroids are the drug of choice in the treatment of optic neuritis. Acute pain due to trigeminal neuralgia can be successfully managed with anticonvulsants such as carbamazepine or phenytoin [166; 167]. Carbamazepine, clonazepam, or amitriptyline is effective in reducing pain resulting from Lhermitte sign or dysesthesias [168; 169]. Both intermittent neuralgias and central pain respond to sodium-channel blockers. Pain associated with clonic muscle spasms may respond to antispasticity agents [102].

Subacute pain is often secondary to the disease; treatment will depend on the condition. Chronic pain is very common and is usually caused by dysesthesias. It is difficult to manage, but carbamazepine, phenytoin, gabapentin, lamotrigine, topiramate, and tricyclic antidepressants are options [102].

Tremor

Tremor is one of the most disabling and difficult to treat neurologic impairments in MS [102]. Available treatments, depending on severity of the tremor, include mechanical damping (e.g., diving weights), high doses of isoniazid (600–1,200 mg/day), clonazepam, beta blockers, or neurosurgery (thalamotomy or thalamic deep brain stimulation). It is important to monitor liver function tests when using high-dose isoniazid, which should be taken in combination with pyridoxine to prevent the development of peripheral neuropathy [102]. Clonazepam is only moderately effective and is limited by sedation. Thalamotomy and deep brain stimulation can provide dramatic short-term results, but often fail because of long-term disease progression.

REHABILITATION

Disease-modifying treatments slow the progression of MS but do not stop it; symptoms will continue to increase. As ultimate cure is as yet unattainable, management of these functional deficits is of utmost importance. Neurorehabilitation together with occupational therapy is the best approach.

Few studies have assessed the effectiveness of neurorehabilitation on outcomes and disease progression in patients with MS, partly because the highly variable and unpredictable nature of the disease course makes such research difficult [170; 171]. Its general effectiveness is well established in conditions such as stroke and head trauma, and it is believed to be of use in cases of MS [172]. Furthermore, even if rehabilitation has no direct influence on disease progression, it has been shown to improve ability to carry out activities of daily living, participation in social activities, and quality of life [173].

A multidisciplinary approach is best when establishing a rehabilitation program for patients with MS [174; 175]. This rehabilitation consists of physiotherapy, cognitive rehabilitation, speech and language therapy, and occupational therapy to control symptoms and disabilities [176; 177]. Cognitive rehabilitation is under the supervision of neuropsychologists, while psychologists and psychiatrists play a key role in the treatment of depression and emotional distress [178; 179]. Several studies have demonstrated that exercise, cognitive therapy and energy conservation instruction have a beneficial effect on self-reported quality of life [180; 181; 182]. Physical therapy, specifically gait training, can result in fatigue reduction [183]. Robotic-assisted, body-weight-supported treadmill training has demonstrated positive impact in rehabilitation of patients with severe walking disabilities, whereas over-ground gait training shows more beneficial effects in patients with less severe impairments [184].

Motor deficits are most often treated with physical and occupational therapy. However, in 2021, the FDA approved a neurostimulation device to address ataxia and other gait disturbances in patients with mild-to-moderate MS [185]. It is a portable, nonimplantable device that delivers mild neuromuscular electrical stimulation to the dorsal surface of the patient's tongue. The device is intended to be used by prescription only as an adjunct to a supervised therapeutic exercise program in patients 22 years of age and older [185].

INDIVIDUAL TREATMENT PLANS

Clinically Isolated Syndrome

As discussed, clinically isolated syndrome is considered one of the earliest clinical presentations of RRMS. Studies have demonstrated that treatment with an immunomodulatory drug (specifically interferon) early in this initial period can decrease the likelihood of developing into symptomatic MS [186; 187; 188]. It is believed that immediate treatment has modest efficacy compared to delayed initiation of treatment [186; 187; 188].

RRMS

Managing attacks or exacerbations is the cornerstone of the treatment of patients with RRMS. An attack of RRMS is defined as the onset of new or exacerbation of existing neurologic symptoms resulting in deterioration of the patient's condition by at least one step on a validated disability status scale that persists for a minimum period of 24 hours and is not related to infection [58]. It is important to remember that even with appropriate and adequate use of drugs, the majority of patients with RRMS will still experience some attacks and many will develop some degree of disability. The aim of treating an acute exacerbation is to reduce the duration and intensity of neurologic impairment. A complete recovery to the baseline level and prevention of long-term disability remains elusive.

It is essential to rule out infection before initiating therapy, as symptoms may be similar, and the most common treatment used for acute attacks (glucocorticoids) can be life-threatening in patients with pre-existing infection [99]. Because most of the immune response in MS occurs early in the disease course, aggressive early treatment with disease-modifying drugs is essential [189]. The choice of agent is usually guided by available evidence, but patient response and tolerability are the most important factors.

The later stages of RRMS tend to be less inflammatory and more degenerative, and treatment during these stages focuses on symptom reduction and quality of life. Immunomodulation with disease-modifying drugs continues, although, as noted, the long-term efficacy is not well established.

Progressive Types

Both SPMS and PRMS are comparatively more difficult to treat than the relapsing forms of MS. Several types of immunosuppressive therapies have shown at least some beneficial effects in the treatment of progressive MS disease. However, these immunosuppressive therapies only briefly halt a rapidly progressive course and are dangerous if prescribed for longer periods [99]. The interventions that have shown some efficacy in progressive types of MS include cyclosporine, total lymphoid radiation, mitoxantrone, methotrexate, interferon, cyclophosphamide, azathioprine, corticosteroids, and IV immunoglobulins [190].

Mitoxantrone is beneficial in patients with SPMS and PRMS and effectively reduces the disease progression and frequency of relapses in patients in short-term follow-up [191]. However, long-term use of this medication causes cardiotoxicity. Rituximab, a monoclonal antibody, is frequently used off-label to treat MS. One study compared the effectiveness and safety of mitoxantrone and rituximab in patients with active relapsing MS [192]. A total of 292 patients were included in the study; 119 received rituximab and 173 received mitoxantrone. While there was no significant effect favoring treatment with either agent, regarding worsening disability or relapse occurrence, treatment with rituximab was associated with a significantly lower probability of severe adverse events [192].

Treatment with interferon leads to fewer relapses and less disease activity. Interferons show a great promise in treating SPMS, but more validation is required for their widespread use [193].

Intravenous cyclophosphamide and glucocorticoid monthly pulses may have a beneficial effect in younger patients with progressive MS. Methotrexate may alter the disease course in patients with SPMS and PPMS, but this is not proven [194].

Until recently, no therapy had been approved specifically for the treatment of PPMS, though several trials have been conducted to assess the potential efficacy of interferons and mitoxantrone, glatiramer acetate, methylprednisolone pulses, and an open-label study of riluzole [195; 196; 197]. As noted, ocrelizumab is now approved for patients with the PPMS subtype.

Benign MS

As discussed, benign MS is mild form of MS in which the patients do not develop any disability. Benign MS is typically treated with one of the disease-modifying drugs immediately after a confirmed MS or clinically isolated syndrome diagnosis [99; 198].

ALTERNATIVE TREATMENTS

Approximately 60% of patients with MS use complementary and alternative medicine. However, with the exception of vitamin D, there is little or no available evidence to support the use of these therapies to improve MS symptoms or disease course [199; 200].

Vitamin D's ability to modulate the immune system may prevent or slow the progression of MS [201]. Results of a study presented at the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) meeting indicated that every 50 nmol/L increase in average serum vitamin D levels translated into a 57% decrease in the rate of new active MS-defining lesions [202]. In fact, the presence of rare variants in CYP27B1, which encodes the enzyme that converts vitamin D to its active form, is strongly associated with MS risk; this supports a causal role of vitamin D deficiency in the development of MS [201]. However, one small study found that high-dose vitamin D supplementation did not result in improvements in symptoms compared to patients with adequate vitamin D [203]. Additionally, results of two clinical trials presented at the 2022 ECTRIMS conference suggest that high doses of vitamin D do not reduce MS disease activity [204; 205]. More research is necessary to determine the role of vitamin D supplementation (e.g., dose, optimum time to initiate therapy) in the treatment of MS.

Some ecologic studies have found a correlation between high intake of polyunsaturated fats and low MS prevalence, and some have suggested that increasing intake of omega fatty acids might improve MS symptoms [206]. However, no specific diet has been shown to have any effect on MS lesions or symptoms [207]. Furthermore, a 2012 trial found no beneficial effects on disease activity with omega-3 fatty acids when compared with placebo as monotherapy or in combination with interferon beta-1a [206].

The use of cannabis to alleviate symptoms of MS remains controversial. Some patients report that smoking cannabis reduces spasticity and other MS-related symptoms [208; 209]. The impairment of neurotransmission seen with MS can be controlled by endocannabinoid receptors and endogenous cannabinoid ligands, which can limit spasticity and may influence the processes that drive the accumulation of progressive disability [210]. However, the cognitive deficit experienced by smoking cannabis that is currently available (e.g., "street" cannabis) may outweigh the benefits [211]. Researchers continue to explore the role of cannabinoids in the treatment of MS symptoms, particularly muscle stiffness and spasms, neuropathic pain, and sleep and bladder disturbance [212].

Derivatives of the herb *Ruta graveolens*, also known as common rue, have been traditionally used to reduce MS symptoms [213]. However, strong evidence of efficacy is lacking.

Bee venom therapy is also believed to have beneficial effects because of its anti-inflammatory properties and possibly its ability to block IL-6 as a pro-inflammatory cytokine, but the research has shown only marginal evidence of benefit [214].

Bee venom therapy can also be potentially lethal because of high risk of anaphylactic shock [199].

Hyperbaric oxygen therapy has been used in patients with MS based on the theory that poor oxygenation of affected nerves may exacerbate symptoms. Studies have demonstrated that hyperbaric oxygenation has no proven benefits on patients with MS [215].

Antioxidants are believed to reduce blood-brain barrier permeability, and levels are reduced in patients with MS [216; 217]. It has been reported that raising uric acid levels protects the integrity of the blood-brain barrier by removing peroxynitrite, an oxidant that is linked to axonal degeneration. Further research is ongoing to explore the role of antioxidants in the treatment of MS [218; 219].

Studies have demonstrated that intestinal parasites such as hookworm may have a protective role against MS by inducing changes in immunoregulation [220]. One study found that the introduction of helminths reduced the number of lesions detected by MRI [221]. Preliminary trials indicate that helminthic therapy is safe, but serious adverse effects are possible.

Yoga and general exercise have been found to reduce fatigue and improve overall quality of life in patients with MS [222]. Small studies of acupuncture in patients with MS have found improvements in pain, muscle spasm, and quality of life [223]. Further clinical trials are necessary to establish efficacy.

ONGOING RESEARCH: POSSIBILITIES FOR FUTURE TREATMENT

Advances in MS treatment have progressed at a rapid pace since 2000. Ongoing research for new treatments is aimed at drugs that:

- Have improved efficacy and are well tolerated
- Target both inflammation and neurodegeneration
- Promote remyelination and repair
- Are conveniently administered, preferably orally
- Effectively treat PPMS
- Effectively treat the chronic symptoms of MS, particularly fatigue
- Improve patient adherence

Alemtuzumab

Alemtuzumab is used for the treatment of RRMS, and researchers continue to explore its efficacy. It is a humanized monoclonal antibody that depletes lymphocytes, causing long-term immunomodulation, and is approved for the treatment of chronic lymphocytic leukemia and T-cell lymphoma. In phase III studies, alemtuzumab showed greater reductions in MS relapse rate and disease activity compared to ß-interferon [224]. It has also shown a beneficial effect on disability progression. Significant side effects include idiopathic thrombocytopenic purpura and Graves' disease.

Daclizumab

Daclizumab is an anti-IL2 monoclonal antibody, originally approved for the prevention of rejection after organ transplantation. In 2016, daclizumab received FDA approval for the treatment of adults with relapsing forms of MS. In 2018, daclizumab was withdrawn from the market, following reports from Germany, the United States, and Spain about the development of inflammatory encephalitis and meningoencephalitis in patients receiving the agent [225; 226].

Tcelna

Tcelna is a therapeutic vaccine against autologous T-cells utilizing myelin-reactive lymphocytes from peripheral blood. A phase IIb trial of Tcelna demonstrated a 55% reduction in annualized relapse rate as compared to placebo [227]. Financial issues experienced by the manufacturer have made research progress slow [228].

The pathogenesis of progressive MS is a complex, multi-level process that causes therapeutic difficulties. Along with variables such as age and duration of the disease, pathogenetic mechanisms change from inflammatory to neurodegenerative processes. This, therefore, limits in time the efficacy of available approved anti-inflammatory drugs (e.g., ocrelizumab, siponimod). Innovative solutions continue to be sought and research studies have been conducted to evaluate the effectiveness of drugs with neuroprotective or remyelinating effects in progressive MS. Among these are biotin, ibudilast, simvastatin, alpha-lipoic acid, clemastine, amiloride, fluoxetine, riluzole, masitinib, opicinumab, and lamotrigine [229; 230; 231; 232].

PROGNOSIS

A number of factors have been identified as potential prognostic indicators in MS, capable of modifying the disease course or predicting exacerbations. These include demographics, type of MS, lesion load, and psychosocial stress.

DEMOGRAPHIC FACTORS

As discussed, White patients, especially of Northern European ancestry, are more susceptible to developing MS, while people living near the equator carry the lowest risk [6]. Although the prevalence of MS is higher among persons of European ancestry than those of African descent (2:1), patients in the latter population group are older at disease onset, more likely to have multiple lesions affecting vision and mobility at diagnosis, and tend to follow a more progressive course [4; 6]. Additionally, susceptibility rates vary among these groups, with recent findings suggesting that African American women have a higher than previously reported risk of developing MS [233].

Older studies suggest that women tend to have a more benign course then men [234]. However, studies have challenged this notion and have concluded that an individual's sex does not determine the disease prognosis independently [235]. A 2019 prevalence study found that MS is three times more common in women than in men, suggesting that hormones may play

a significant role in determining susceptibility to MS [236]. Younger age at disease onset has a better prognosis compared with late onset [234]. One study observed that disability in MS is correlated more with the patient's age of onset than disease subtype (i.e., relapsing or progressive) [237; 238].

SUBTYPE OF MS

The relapsing form of MS has a much more favorable prognosis compared with progressive disease [234; 235]. One observational study showed that patients with a progressive form of MS acquired irreversible disability earlier compared to patients with relapsing-remitting onset [239]. After irreversible disability occurred, however, the time course of progressive disability was similar in the two groups. Data have suggested that the development of a progressive course in patients with MS may be the most important prognostic factor [240].

EARLY SYMPTOMS

In the past, the presence of specific MS symptoms at disease onset was thought to predict the disease course; for example, sensory symptoms and optic neuritis indicate a favorable prognosis, while pyramidal, brainstem, and cerebellar symptoms portend an unfavorable prognosis [234]. However, subsequent studies have observed that this theory is false and the onset symptoms are not independent prognostic factors [235; 241]. An observational study found that clinical variables assessed early in RRMS predicted time to irreversible disability (i.e., Expanded Disability Status Scale score of 4 or limited walking without aid); however, this was not true for subsequent disability progression [242]. Data from a large clinical trial cohort showed that younger patients (38 years of age or younger) with high baseline relapses and MRI lesion burden have the highest risk of subsequent disease activity [243].

LESION LOAD

A serial MRI study observed a strong relationship between the development of lesions early in the disease course and long-term disability [244]. The correlation seems to plateau at higher levels of disability, indicating that MRI lesion burden is a poor determinant of disease progression in patients with advanced disease. A pooled data study showed that MRI lesion load is weakly correlated with age at disease onset, duration of the disease, and disease progression [245].

PSYCHOSOCIAL STRESS

Some studies have suggested that MS relapses may be more frequent after stressful life events, although others have found no relationship between MS exacerbations and life-event stress [246; 247]. It appears that the number, not the severity, of stressful life events is most important. The results of a 2022 study suggest that the coupling of blunted central stress processing and blunted immune system sensitivity to stress hormones are related to key severity measures of MS [248]. The exact mechanism of a relationship between stress and MS exacerbations is still unknown. Stress management therapy may have a beneficial effect in reducing the development of new MRI brain lesions while patients are in treatment [249].

PREGNANCY AND MS

MS is more prevalent in women of child-bearing age, and pregnancy can pose a challenge in the management of MS [250]. As stated, the incidence of MS has increased, with a corresponding higher female-to-male ratio [236; 251; 252]. These factors emphasize the need for more research in the subject of pregnancy in women with MS. Previously, women with MS were discouraged from having children, but this has not been supported by evidence. Today, pregnancy is believed to have no adverse effect on the course and prognosis of MS [253; 254].

The significant hormonal changes that occur during pregnancy result in a physiologic shift from T-helper 1 to T-helper 2 immune response, leading to an increase in anti-inflammatory cytokines [255]. This shift is partly responsible for the reduction in MS relapses in pregnant women [256]. The increase in estrogen levels during this period also suppresses T-cell proliferation and cytokine production [257; 258]. Alpha-fetoprotein, which is produced by the liver and yolk sac of a developing fetus, decreases neuroinflammation and disease severity [259]. Overall, pregnancy appears to have a beneficial effect on MS disease activity.

There is no evidence that MS affects fertility and conception [253; 254]. However, patients with MS have a high rate of sexual dysfunction that may be associated with a number of neurologic symptoms and disabilities [260]. These factors can adversely affect the overall quality of sexual life and impede conception [261].

In cases of very aggressive MS, there is a risk of inadequate maternal care. Therefore, adequate disease control should be achieved prior to pregnancy. Women with MS who are pregnant or considering pregnancy are often concerned about the genetic transmission of MS to their child. The absolute risk of disease transmission ranges from 2% to 4%, but there are no genetic or prenatal screening tests that can detect MS [262].

TREATMENT DURING PREGNANCY

If safe, women intending to conceive should stop their MS treatment for at least three months prior to conception. A study conducted in Sweden concluded that pregnancies that were not exposed to the ß-interferon in utero for at least a two-week period prior to conception resulted in healthier infants than pregnancies with such exposure [263]. A small Canadian study found that pregnancies exposed to ß-interferon resulted in a higher number of miscarriages, low birth weight, and prematurity [264]. However, a larger study did not find a significantly higher rate of complications in pregnancies accidentally exposed to immunomodulators [265]. In general, even the higher incidence of complications observed in some studies was only slightly greater than that of the general population. If continued treatment is necessary, modifications to the prescribed regimen (with preference for lower risk options) may be necessary. Many drugs used to treat MS and its related symptoms are contraindicated during pregnancy.

For disease modification, the safest options are glatiramer acetate and immunoglobulin, which appear to do no harm to the fetus and are pregnancy category B. ß-interferons, mitoxantrone, and corticosteroids are pregnancy category C, as animal studies have demonstrated adverse effects to the fetus. The risk-benefit ratio should be considered prior to using these medications in pregnant women. Category D drugs, which have evidence of fetal risk and should only be considered in life-threatening situations or when safer drugs are ineffective, include azathioprine, cyclophosphamide, and mitoxantrone. Category X drugs such as methotrexate pose an extremely high risk to the fetus and should not be used for women who are or may become pregnant.

Apart from immunomodulatory or immunosuppressive agents, the medications used to control the symptoms of MS should also be reconsidered. Oxybutynin and pemoline, prescribed for incontinence and fatigue respectively, are pregnancy category B, and their continued use should be safe. Many of the drugs used in the treatment of MS are category C, including:

- Gabapentin and carbamazepine for paroxysmal disorders
- Amantadine and potassium channel blockers for fatigue
- Selective serotonin reuptake inhibitors for depression
- Baclofen and dantrolene for spasticity

Benzodiazepines and phenytoin (used for pain and insomnia) are category D and should be avoided. Fingolimod or natalizumab may pose a risk of rebound disease activity after stopping the medication for pregnancy [266].

Unplanned pregnancy, without proper adjustment of treatment, carries a high inherent risk to the fetus. As such, women should be counseled to discuss childbearing plans with their physician prior to conception and to maintain adequate birth control if pregnancy is not desired.

MS AND DELIVERY

There is no evidence that MS leads to an increased number of spontaneous abortions (miscarriage), stillbirths, or congenital malformations. Several studies of large numbers of women have repeatedly demonstrated that pregnancy, labor, delivery, and the incidence of fetal complications are no different in women who have MS than in women who do not have MS [254].

The mode of delivery is guided by obstetric indications rather than the presence of MS. However, a study conducted in the United States found that the rate of non-vaginal delivery was higher among women with MS than the general population [267]. If cesarean delivery is necessary, proper attention should be provided during preoperative evaluation to reduce postoperative neurologic complications. During labor, epidural injection is considered to be a safer option than spinal block for anesthesia in patients with MS, as spinal block is suspected to be associated with neurotoxic effects [268; 269]. Autonomic dysreflexia, a very rare, potentially life-threatening condition related to spinal cord lesions, can arise in women with MS during delivery [270]. Patients should be duly informed about the type of anesthesia and its possible side effects and complications.

RELAPSE RISK AFTER DELIVERY

The rate of MS relapse increases after delivery. One study observed that a rapid increase in the number of interferon-γ-producing T-cells may be responsible for the increased risk of relapse [271]. Women with higher Expanded Disability Status Scale scores and higher relapse rates before pregnancy tend to have a greater risk of relapse during the postpartum period [272].

BREASTFEEDING

As with all women, the rate of breastfeeding among women with MS varies widely and depends upon various factors. Several studies have demonstrated a possible beneficial effect of breastfeeding on postpartum relapse rates, but the higher risk of relapses during the postpartum period may make breastfeeding difficult or impossible, especially if adequate treatment with immunomodulatory or immunosuppressive agents is indicated [273]. Studies have found an increased risk of relapse in the first three months postpartum, with disease stability prior to pregnancy considered a primary factor in reducing this risk. However, a 2020 study found no increased relapse rate in the postpartum period and suggests that exclusive breastfeeding may contribute to this reduced risk [274]. There is insufficient information regarding the levels of many MS drugs in human milk.

CONCLUSION

MS is a relatively uncommon disease, but the effects can be devastating for patients. Unfortunately, a cure is elusive, and the cause is still unknown. Different MS subtypes are being described, and healthcare providers should stay abreast of the different clinical presentations, effective management, and progression of the disease. There is also a need for healthcare providers to be able to communicate with and educate patients regarding important treatment options available and disease prognosis. At every follow-up visit, healthcare professionals should encourage their patients to participate actively in decision-making and self-management. Although a variety of specialists is often involved in the care of individuals with MS, the primary care team has a pivotal role in the overall management of these patients. Rapid strides have been made in the understanding MS, and without a doubt one can say that the future holds better prospects for patients with this debilitating disease.

Customer Information/Answer Sheet/Evaluation insert located between pages 64–65.

COURSE TEST
#98593 MULTIPLE SCLEROSIS

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 December 31, 2025.

1. Geographically speaking, the lowest risk of developing multiple sclerosis (MS) is noted in persons living
- A) *near the equator.*
- B) *in the extreme north.*
- C) *in the extreme south.*
- D) *in developed countries.*

2. MS lesions
- A) *occur only in the brain.*
- B) *cluster near the ventricles.*
- C) *cluster in the peripheral nerves.*
- D) *occur primarily in the gray matter.*

3. The demyelination that underlies MS
- A) *impairs nerve transmission.*
- B) *bolsters the immune attack on oligodendrocytes.*
- C) *causes perpetuation of the proinflammatory condition.*
- D) *permits leukocytes to enter the central nervous system (CNS).*

4. Spasticity associated with MS
- A) *is never painful.*
- B) *does not usually affect ambulation.*
- C) *usually affects the muscles of the trunk and face.*
- D) *is more prominent in the lower extremities than the upper extremities.*

5. MS pain is mainly
- A) *visceral.*
- B) *somatic.*
- C) *neuropathic.*
- D) *musculoskeletal.*

6. The most common ophthalmologic symptom of MS is
- A) *astigmatism.*
- B) *optic neuritis.*
- C) *upbeat nystagmus.*
- D) *intranuclear ophthalmoplegia.*

7. The most common type of MS is
- A) *benign.*
- B) *malignant.*
- C) *relapsing-remitting.*
- D) *primary progressive.*

8. Primary progressive MS is characterized by
- A) *alternating series of clearly defined relapses followed by remissions.*
- B) *steady disease progression with occasional remissions and temporary minor improvements.*
- C) *a long-term absence of symptoms with no functional impairments 15 years after disease onset.*
- D) *progressive neurologic impairment between relapses without any well-defined periods of remission.*

9. Malignant MS
- A) *occurs most commonly in older adults.*
- B) *is also known as Uhthoff phenomenon.*
- C) *is associated with smaller lesions involving the cervical spine.*
- D) *results in major disability and usually death within one year of onset.*

10. Early-onset MS
- A) *accounts for the majority of MS cases.*
- B) *is usually characterized by a relapsing-remitting course.*
- C) *is only diagnosed in patients younger than 10 years of age.*
- D) *most commonly presents with motor, rather than sensory, symptoms.*

Test questions continue on next page →

11. In a patient with MS, a positive Halmagyi-Curthoys head impulse test is indicative of
- A) *optic neuritis.*
- B) *loss of proprioception.*
- C) *lesions on the cervical spine.*
- D) *peripheral vestibular disease.*

12. Most MS lesions within the spinal cord are located in the
- A) *central cord.*
- B) *dorsal columns.*
- C) *lateral corticospinal tract.*
- D) *lateral spinothalamic tract.*

13. Which of the following signs/symptoms should raise suspicion that a condition other than MS is the underlying cause?
- A) *Progressive from onset*
- B) *Lack of peripheral symptoms*
- C) *Abnormal neurologic examination*
- D) *MRI abnormalities in multiple locations*

14. Treatment of the acute exacerbations seen with the relapsing types of MS relies primarily on
- A) *interferons.*
- B) *corticosteroids.*
- C) *adrenocorticotropic hormone (ACTH).*
- D) *Both B and C*

15. The first-line treatment of an MS exacerbation is
- A) *80–120 units ACTH for one to three weeks.*
- B) *IV methylprednisolone (1 g) for five to seven days.*
- C) *44 mcg β-interferon subcutaneously three times per week.*
- D) *500–1,250 mg oral prednisone daily divided for three to seven days.*

16. Plasmapheresis is indicated for patients with MS with
- A) *a malignant course.*
- B) *few current signs of disease.*
- C) *progressive (primary or secondary) course.*
- D) *severe relapses who have failed to respond to IV corticosteroids.*

17. Mitoxantrone is considered one of the most effective drugs in resolving MS relapses, but its use is limited by the risk for
- A) *leukemia and cardiotoxicity.*
- B) *liver and thyroid dysfunction.*
- C) *injection site reactions and lipoatrophy.*
- D) *infusion-related hypersensitivity and anaphylaxis.*

18. The drug of choice for the treatment of MS-related spasticity is
- A) *baclofen.*
- B) *tizanidine.*
- C) *dantrolene.*
- D) *gabapentin.*

19. All of the following behavioral interventions are recommended for patients with MS and nocturia, EXCEPT:
- A) *Avoiding alcoholic beverages*
- B) *Avoiding spicy and acidic foods*
- C) *Increasing caffeine consumption*
- D) *Decreasing fluid intake two to three hours prior to bedtime*

20. Women with MS who are intending to conceive should
- A) *continue their treatment without pause.*
- B) *stop treatment for no more than one month prior to conception.*
- C) *be warned that pregnancy can dramatically worsen MS symptoms.*
- D) *stop treatment for at least three months prior to conception, if safe.*

Be sure to transfer your answers to the Answer Sheet insert located between pages 64–65.
PLEASE NOTE: Your postmark or facsimile date will be used as your test completion date.

Course Availability List

These courses may be ordered by mail on the Customer Information form located between pages 64–65.
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MODERATE SEDATION
#40953 • 5 Credits
Book By Mail – $43 • ONLINE – $35
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.
Faculty: Lori L. Alexander, MTPW, ELS, MWC
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

PROFESSIONAL BOUNDARIES AND SEXUAL MISCONDUCT IN MEDICINE
#41170 • 3 Credits
Book By Mail – $29 • ONLINE – $21
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.
Faculty: Mary Franks, MSN, APRN, FNP-C
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.

RISK MANAGEMENT
UPDATE
#41473 • 5 Credits
Book By Mail – $43 • ONLINE – $35
Purpose: With patient safety as the priority, risk management should focus on the avoidance of medical errors, as they are, along with inadequate informed consent, the most common assertions in malpractice claims in the United States. The purpose of this course is to provide healthcare professionals with the information necessary to engage in risk management practices, including a variety of proven strategies to avoid malpractice.
Faculty: Lori L. Alexander, MTPW, ELS, MWC
Audience: This course is designed for physicians, physician assistants, and nurse practitioners seeking to enhance their knowledge of risk management strategies, especially in the outpatient setting.
Additional Approvals: ABIM, ABS, ABA, ABP, ABPath

ISCHEMIC STROKE
UPDATE
#90284 • 10 Credits
Book By Mail – $78 • ONLINE – $70
Purpose: 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.
Faculty: Lori L. Alexander, MTPW, ELS, MWC
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

AGITATION, SEDATION, AND DELIRIUM IN ADULT ICU PATIENTS
NEW!
#90180 • 5 Credits
Book By Mail – $43 • ONLINE – $35
Purpose: The purpose of this course is to provide prescribers and other healthcare professionals with the knowledge and skills necessary to identify and act to avoid or address agitation, inappropriate sedation, and delirium in ICU patients.
Faculty: Beth Johnston, PharmD, BCPS
Audience: This course is designed for physicians, physician assistants, and nurses involved in the care of patients in intensive care units.
Additional Approvals: ABIM, ABS, ABA

FALLS AND FALL PREVENTION
NEW!
#91660 • 3 Credits
Book By Mail – $29 • ONLINE – $21
Purpose: The purpose of course is to provide healthcare professionals with the knowledge and skills necessary to intervene to reduce falls risk in their patients.
Faculty: Mary Franks, MSN, APRN, FNP-C
Audience: This course is designed for physicians, physician assistants, nurses, and allied professionals involved in the care of patients at risk for falls.
Additional Approvals: ABIM, ABS

Course Availability List *(Cont'd)*

MONKEYPOX: THE 2022 GLOBAL OUTBREAK

Trending

#94040 • 3 Credits

Book By Mail – $29 • ONLINE – $21

Purpose: The purpose of this course is to address these knowledge gaps to enable timely diagnosis, treatment, and prevention of monkeypox, thereby promoting public health strategies to limit spread of the outbreak.
Faculty: John M. Leonard, MD
Audience: This course is designed for physicians, physician assistants, nurses, pharmacy professionals, and other healthcare professionals who may identify and care for patients with suspected or confirmed human monkeypox infection.
Additional Approvals: ABIM, ABS, ABP, ABPath

NECK PAIN IN ADULTS

#94131 • 10 Credits

Book By Mail – $78 • ONLINE – $70

Purpose: The purpose of this course is to provide primary care clinicians with the best available evidence on the clinical management of patients with acute or chronic neck pain.
Faculty: Mark Rose, BS, MA, LP
Audience: This course is designed for all members of the interprofessional healthcare team involved in the care of patients with neck pain.
Additional Approvals: ABIM, ABS, ABA

PHARMACOLOGIC AND MEDICAL ADVANCES IN OBESITY MANAGEMENT

NEW!

#94280 • 15 Credits

Book By Mail – $113 • ONLINE – $105

Purpose: The purpose of this course is to ensure that providers have current and accurate knowledge regarding the available pharmacologic and surgical options to improve outcomes among their patients, with the ultimate goal of improving patient care and outcomes.
Faculty: Mark Rose, BS, MA, LP
Audience: This course is designed for all physicians, nurses, and allied professionals involved in the care of patients who are overweight or obese.
Additional Approvals: ABIM, ABS, ABA, ABP, ABPath

HIV/AIDS: UPDATE FOR FLORIDA

FL Mandate

#94723 • 1 Credit

Book By Mail – $23 • ONLINE – $15

Purpose: HIV infection is now endemic in the United States and throughout much of the world, and HIV/AIDS has become less about cure and more about management and control. As with most chronic diseases, treatment protocols and management strategies change over time. The purpose of this course is to provide a basic, practical review and update of knowledge concerning HIV/AIDS, addressing the key issues that impact clinical care and public health practice.
Faculty: Jane C. Norman, RN, MSN, CNE, PhD; John M. Leonard, MD
Audience: This course is designed for all Florida nurses, physicians, and allied healthcare professionals involved in the care of patients with HIV/AIDS.
Additional Approvals: ABIM, ABS, ABA, ABP, ABPath
Special Approvals: This course fulfills the Florida requirement for 1 hour of HIV/AIDS education.

SUBSTANCE USE DISORDERS AND PAIN MANAGEMENT: DEA MATE ACT TRAINING

DEA MATE Act

#95300 • 8 Credits

Book By Mail – $77 • ONLINE – $69

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

ALZHEIMER DISEASE

UPDATE

#96154 • 15 Credits

Book By Mail – $113 • ONLINE – $105

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

Course Availability List *(Cont'd)*

ATTENTION DEFICIT HYPERACTIVITY DISORDER

UPDATE

#96214 • 5 Credits

Book By Mail – $43 • ONLINE – $35

Purpose: Attention deficit hyperactivity disorder (ADHD) has a significant effect on day-to-day functioning and quality of life; however, it often goes unrecognized. The purpose of this course is to educate healthcare professionals about the epidemiology, diagnosis, and management of ADHD.

Faculty: John J. Whyte, MD, MPH; Paul Ballas, DO

Audience: This course is designed for all physicians, nurses, and social work/counseling groups involved in the care of patients with attention deficit hyperactivity disorder.

Additional Approvals: ABIM, ABS, ABP

SUICIDE ASSESSMENT AND PREVENTION

#96442 • 6 Credits

Book By Mail – $50 • ONLINE – $42

Purpose: The purpose of this course is to provide health and mental health professionals with an appreciation of the impact of depression and suicide on patient health as well as the skills necessary to identify and intervene for patients at risk for suicide.

Faculty: Mark Rose, BS, MA, LP

Audience: This course is designed for physicians, nurses, pharmacists, and other healthcare professionals who may identify persons at risk for suicide and intervene to prevent or manage suicidality.

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

PALLIATIVE CARE AND PAIN MANAGEMENT AT THE END OF LIFE

UPDATE

#97384 • 15 Credits

Book By Mail – $113 • ONLINE – $105

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 challenges, benefits, and strategies of optimum palliative care at the end of life.

Faculty: Lori L. Alexander, MTPW, ELS, MWC

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

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

CANNABINOID OVERVIEW

NEW!

#98010 • 3 Credits

Book By Mail – $29 • ONLINE – $21

Purpose: The purpose of this course is to provide healthcare professionals in all practice settings the knowledge necessary to increase their understanding of the various cannabinoids.

Faculty: Chelsey McIntyre, PharmD

Audience: This course is designed for healthcare professionals whose patients are taking or are interested in taking cannabinoid products.

Additional Approvals: ABIM, ABS

TOP-SELLING HERBAL SUPPLEMENTS

#98080 • 3 Credits

Book By Mail – $29 • ONLINE – $21

Purpose: The purpose of this course is to provide healthcare professionals in all practice settings the knowledge necessary to increase their understanding of the most popular herbal supplements and to better counsel patients regarding their use.

Faculty: Chelsey McIntyre, PharmD

Audience: This course is designed for healthcare professionals whose patients are taking or are interested in taking herbal supplements.

Additional Approvals: ABIM, ABS, ABP

SUPPLEMENTS FOR AGING

NEW!

#98190 • 5 Credits

Book By Mail – $43 • ONLINE – $35

Purpose: The purpose of this course is to provide healthcare professionals in all practice settings the knowledge necessary to increase their understanding of the supplements that may be used by their older adult patients.

Faculty: Chelsey McIntyre, PharmD

Audience: This course is designed for healthcare professionals whose older patients are taking or are interested in supplements.

Additional Approvals: ABIM, ABS

NATURAL PSYCHEDELICS

NEW!

#98320 • 3 Credits

Book By Mail – $29 • ONLINE – $21

Purpose: The purpose of this course is to provide healthcare professionals with an increased understanding of natural psychedelics and the considerations associated with the safety, effectiveness, and legal use of these substances.

Faculty: Chelsey McIntyre, PharmD

Audience: This course is designed for healthcare professionals whose patients are taking or have questions about natural psychedelic products.

Additional Approvals: ABIM, ABS

Course Availability List *(Cont'd)*

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

#98813 • 10 Credits

Book By Mail – $78 • ONLINE – $70

Purpose: The purpose of this course is to provide healthcare professionals a current review of pathogenesis, diagnosis, assessment, and treatment of chronic obstructive pulmonary disease (COPD), emphasizing strategies for prevention and best practice clinical guidelines for managing the stable patient and COPD exacerbations.
Faculty: John M. Leonard, MD
Audience: This course is designed for physicians, primary care providers, nurses, respiratory therapists, and medical assistants involved in the care of patients with COPD.
Additional Approvals: ABIM, ABS, ABA

SLEEP DISORDERS

#98883 • 10 Credits

Book By Mail – $78 • ONLINE – $70

Purpose: Many of the complications associated with sleep disorders are preventable, making early diagnosis and appropriate treatment vital. The purpose of this course is to provide healthcare professionals with the information necessary to identify and effectively treat sleep disorders, thereby improving patients' quality of life and preventing possible complications.
Faculty: Teisha Phillips, RN, BSN
Audience: This course is designed for all healthcare professionals, including physicians, nurses, pharmacists, and mental health practitioners, who are involved in the care of patients experiencing a sleep-related disorder.
Additional Approvals: ABIM, ABS, ABA, ABP

ANEMIA IN THE ELDERLY

#99084 • 5 Credits

Book By Mail – $43 • ONLINE – $35

Purpose: The purpose of this course is to provide primary care health professionals a review of pathophysiology, clinical assessment, and management of anemia in the elderly. The goal is to promote early diagnosis, appropriate treatment, and improved outcomes for the geriatric population.
Faculty: Susan Waterbury, MSN, FNP-BC, ACHPN
Audience: This course is designed for physicians, physician assistants, nurses, and other healthcare professionals involved in the care of elderly patients.
Additional Approvals: ABIM, ABS, ABPath

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

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	97923	Domestic Violence: The Florida Requirement / 2 Credits	$15
	90120	Pulmonary Embolism / 2 Credits	$15
	91152	Strategies for Appropriate Opioid Prescribing: The Florida APRN/PA Req. / 3 Credits	$21
	94820	Chronic Cough in Adults / 10 Credits	$70
	98593	Multiple Sclerosis / 10 Credits	$70

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☐	41170	Prof. Boundaries & Sexual Misconduct in Medicine / 3	$29	☐	96214	Attention Deficit Hyperactivity Disorder / 5	$43
☐	41473	Risk Management / 5	$43	☐	96442	Suicide Assessment and Prevention / 6	$50
☐	90284	Ischemic Stroke / 10	$78	☐	97384	Palliative Care and Pain Mgmt at the End of Life / 15	$113
☐	90180	Agitation, Sedation, & Delirium in Adult ICU Pts / 5	$43	☐	98010	Cannabinoid Overview / 3	$29
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Answer Sheet

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Please note the following:

- In accordance with the *AMA PRA Category 1 Credit™* system, learners 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.

#91334 MEDICAL ERROR PREVENTION AND ROOT CAUSE ANLAYSIS—2 CE CREDITS Please refer to pg 13.

Expiration Date: 08/31/25 *May be taken individually for $15*

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

#97923 DOMESTIC VIOLENCE: THE FLORIDA REQUIREMENT—2 CE CREDITS Please refer to pg 24.

Expiration Date: 07/31/25 *May be taken individually for $15*

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

#90120 PULMONARY EMBOLISM—2 CE CREDITS Please refer to pgs 35–36.

Expiration Date: 08/31/26 *May be taken individually for $15*

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

#91152 STRATEGIES FOR APPROPRIATE OPIOID PRESCRIBING: THE FL APRN/PA REQ.—2 CE CREDITS Please refer to pgs 52–53.

Expiration Date: 08/31/25 *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 86–87.

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.	❍	❍	❍	❍

#98593 MULTIPLE SCLEROSIS—10 CREDITS Please refer to pages 123–124.

Expiration Date: 12/31/25 *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.	❍	❍	❍	❍

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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?
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?

#91334 2 Credits	#97923 2 Credits	#90120 2 Credits	#91152 3 Credits	#94820 10 Credits	#98593 10 Credits
1. ☐ New ☐ Review	1. ☐ New ☐ Review	1. ☐ New ☐ Review	1. ☐ New ☐ Review	1. ☐ New ☐ Review	1. ☐ New ☐ Review
2. ____ Hours	2. ____ Hours	2. ____ Hours	2. ____ Hours	2. ____ Hours	2. ____ Hours
3. ☐ Yes ☐ No	3. ☐ Yes ☐ No	3. ☐ Yes ☐ No	3. ☐ Yes ☐ No	3. ☐ Yes ☐ No	3. ☐ Yes ☐ No
4. ☐ Yes ☐ No	4. ☐ 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	5. ☐ Yes ☐ No	5. ☐ Yes ☐ No
6. ☐ Yes ☐ No	6. ☐ 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	7. ☐ Yes ☐ No	7. ☐ Yes ☐ No
8. ☐ Yes ☐ No	8. ☐ 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	9. ☐ Yes ☐ No	9. ☐ Yes ☐ No
10. ☒ N/A	10. ☐ Yes ☐ No	10. ☐ Yes ☐ No	10. ☐ Yes ☐ No	10. ☐ Yes ☐ No	10. ☐ Yes ☐ No
11. ☐ Yes ☐ No	11. ☐ Yes ☐ No	11. ☐ Yes ☐ No	11. ☐ Yes ☐ No	11. ☐ Yes ☐ No	11. ☐ Yes ☐ No
12. ☐ Yes ☐ No	12. ☐ 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	13. ☐ Yes ☐ No	13. ☐ Yes ☐ No

#91334 Medical Error Prevention and Root Cause Analysis — If you answered YES to question #12, how specifically will this activity enhance your role as a member of the interdisciplinary team? _____

#97923 Domestic Violence: The Florida Requirement — If you answered YES to question #12, how specifically will this activity enhance your role as a member of the interdisciplinary team? _____

#90120 Pulmonary Embolism — If you answered YES to question #12, how specifically will this activity enhance your role as a member of the interdisciplinary team? _____

#91152 Strategies for Appropriate Opioid Prescribing: The Florida APRN/PA Requirement — If you answered YES to question #12, how specifically will this activity enhance your role as a member of the interdisciplinary team? _____

#94820 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? _____

#98593 Multiple Sclerosis — If you answered YES to question #12, how specifically will this activity enhance your role as a member of the interdisciplinary team? _____

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