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CME FOR
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# Medical Error Prevention and Root Cause Analysis

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

**In addition to receiving *AMA PRA Category 1 Credit™*, physicians participating in Maintenance of Certification will receive the following points appropriate to their certifying board: 2 ABIM MOC Points, 2 ABS MOC Points, 2 ABA MOC Points, 2 ABP MOC Points, 2 ABPath CC Points.**

### *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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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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***Special Approvals***
This activity is designed to comply with the requirements of California Assembly Bill 1195, Cultural and Linguistic Competency, and California Assembly Bill 241, Implicit Bias.

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

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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 interven-tion 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 under-recognized 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 find-

  

ings, 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 2022, the Florida Board of Medicine has determined the five most misdiagnosed conditions to be [29]:

- Cancer-related conditions
- Gastroenterology-related issues
- Cardiology-related issues
- Neurologic conditions
- Missed spinal cord compression

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

### Cancer

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].

### Neurologic/Spinal Cord-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.

**Missed Spinal Cord Compression**

Epidural compression syndrome is an umbrella term that encompasses spinal cord compression, cauda equina syndrome, and conus medullaris syndrome. While these conditions differ in the level of neurologic deficit at presentation, they are otherwise similar in symptoms, evaluation, and management. Massive herniation of a midline disk, typically at the L4 to L5 disk level, is the most common cause of epidural compression syndrome. Tumor, epidural abscess, spinal canal hematoma, or lumbar spine spondylosis represent other causes [37].

Spinal cord compression is often secondary to herniated disk, vertebral fracture, or space-occupying lesion. Missing this diagnosis, typically by attributing the associated pain to muscle or nerve causes, will miss potentially catastrophic conditions [38; 39; 40; 41]. In a study of 3,786 individuals, the estimated prevalence of asymptomatic spinal cord compression in a healthy population was 24.2%, with a significantly higher prevalence in older populations compared with younger populations and American/European populations compared with Asian populations [42].

In patients with spinal cord compression, neurologic status at diagnosis is the greatest predictor of ultimate neurologic outcome and underscores the importance of early accurate diagnosis. The dominant symptom is back pain with accelerating pain severity. Pain from epidural spinal cord compression is made worse with recumbent positioning, and unilateral or bilateral radiculopathy may develop over time. For many patients, leg pain or neurologic symptoms are more dominant than back pain. Also common at diagnosis is symmetrical lower extremity weakness that may have progressed to gait disturbance or paralysis. Decreased lower extremity reflexes are associated with cauda equina syndrome [37].

## 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.**

**In addition to receiving *AMA PRA Category 1 Credit™*, physicians participating in Maintenance of Certification will receive the following points appropriate to their certifying board: 2 ABIM MOC Points, 2 ABS MOC Points, 2 ABA MOC Points.**

***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 appears at the end of this course.)

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

***Faculty Disclosure***
Contributing faculty, 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.

EVIDENCE-BASED PRACTICE RECOMMENDATION

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].

  

## FACULTY BIOGRAPHIES

**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.

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

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

**Customer Information/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.***

  

# Strategies for Appropriate Opioid Prescribing: The Florida Requirement

**This course, offered by the NetCE Physicians Professional Association, is approved by the Florida Board of Medicine to fulfill the Florida requirement for 2 hours on the safe and effective prescribing of controlled substance medications.**

**In addition to receiving *AMA PRA Category 1 Credit™*, physicians participating in Maintenance of Certification will receive the following points appropriate to their certifying board: 2 ABIM MOC Points, 2 ABS MOC Points, 2 ABA MOC Points, 2 ABP MOC Points, 2 ABPath CC Points.**

### *Audience*

This course is designed for all physicians and osteopath physicians 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.

### *Division Planner*

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.

### *Accreditations & Approvals*

In support of improving patient care, NetCE is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

### *Designations of Credit*

NetCE designates this enduring material for a maximum of 2 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 2 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit. Completion of this course constitutes permission to share the completion data with ACCME.

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

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

Successful completion of this CME activity, which includes participation in the activity with individual assessments of the participant and feedback to the participant, enables the participant to earn 2 MOC points in the American Board of Pediatrics' (ABP) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABP MOC credit.

This activity has been designated for 2 Lifelong Learning (Part II) credits for the American Board of Pathology Continuing Certification Program.

Through an agreement between the Accreditation Council for Continuing Medical Education and the Royal College of Physicians and Surgeons of Canada, medical practitioners participating in the Royal College MOC Program may record completion of accredited activities registered under the ACCME's "CME in Support of MOC" program in Section 3 of the Royal College's MOC Program.

### *Special Approvals*

This activity is designed to comply with the requirements of California Assembly Bill 1195, Cultural and Linguistic Competency, and California Assembly Bill 241, Implicit Bias.

This course, offered by the NetCE Physicians Professional Association, is approved by the Florida Board of Medicine to fulfill the Florida requirement for 2 hours on the safe and effective prescribing of controlled substance medications.

### *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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### *Disclosure Statement*

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


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

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

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 [7]. 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 [8]. 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 [9]. 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 [8].

In 2011, the American Society of Addiction Medicine (ASAM) published their latest revision in defining the disease of addiction. In 2018, ASAM's board recognized the need for an updated definition of addiction that would be more accessible to its stakeholder groups, including patients, the media, and policymakers. Accordingly, the Board appointed a Task Force that revised the definition of addiction for use in ASAM's policy statements. The revised 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.

## 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]. This is refuted by the following data showing that national opioid analgesic prescribing and overdose peaked in 2011 and are in multiyear decline.

According to a 2019 report from the National Forensic Laboratory Information System (NFLIS), prescription reports for hydrocodone increased dramatically from 2001 to 2010, but then steadily decreased through 2019. Oxycodone reports increased steadily from 2001 to 2004, and again from 2006 to 2010, and then steadily declined through 2019 [18]. Methadone prescribing data were not captured in the report.

Opioid analgesic-associated overdose fatalities have also decreased since 2011, despite published Centers for Disease Control and Prevention (CDC) data reporting a sharp rise in opioid analgesic fatalities in 2014 [19]. This increase was the result of the CDC adding clandestine fentanyl fatalities to figures for prescription opioids in 2014, a difference of more than 4,000 fatalities [20]. The CDC acknowledged this and presented revised 2014 figures with clandestine fentanyl overdoses removed, which supports the belief that opioid analgesic-associated overdose fatalities peaked in 2011 [21; 22; 23]:

  

- 2011: 16,917 fatalities
- 2013: 16,235 fatalities
- 2014: 14,000 fatalities

In addition, some heroin overdose fatalities are misclassified as morphine fatalities. The metabolite unique to heroin, 6-monoacetylmorphine (6-MAM), quickly breaks down into morphine, and medical examiners may be reluctant to label a death heroin-related without 6-MAM present [24]. In 2014, fatal heroin overdoses increased 26% from 2013, and heroin deaths mistakenly attributed to morphine may also have increased during this period [19].

Opioid analgesic prescribing in the United States has declined from the 2011 peak but remains substantially higher than 1990. Before 1990, physicians seldom prescribed opioids for chronic noncancer pain. By the mid-2000s, 1 of 25 adults was prescribed an opioid for chronic pain, and annual opioid analgesic sales totaled more than $9 billion [25]. 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; 26].

Worldwide consumption of opioid analgesics has increased dramatically in 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 [25]. In 2010, the United States had 4.5% of the world population but consumed 80% of global opioid supplies and 99% of hydrocodone supplies [27]. This is partially because access to opioid analgesics is virtually or entirely non-existent for 5.8 billion people worldwide (80%) and highly restricted for 4.1% of the world population [28]. Other countries with adequate opioid access prefer dihydrocodeine or low-dose morphine over hydrocodone for use in moderate or moderately severe pain [29].

Many prescribed opioid analgesic fatalities result from the co-ingestion central nervous system (CNS)/respiratory depressants (especially benzodiazepines) or prescribed methadone. According to the National Institute on Drug Abuse (NIDA), deaths involving benzodiazepines rose from 1,135 in 1999 to 11,537 in 2017. In 2019, 16% of persons who died of an opioid overdose also tested positive for benzodiazepines [30; 31]. 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% [32]. 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 [33]. This is significant considering that dispensed benzodiazepine prescriptions increased 226% between 2009 and 2014 [34]. Additionally, many users obtain benzodiazepines by getting prescriptions from more than one doctor, forging prescriptions, or buying the drugs illicitly. Alprazolam and clonazepam are the two most frequently encountered benzodiazepines on the illicit market [18].

## 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 [35; 36]. On average, from 2017 to 2019, opioids accounted for 79.4% of fatal drug overdoses [35]. In 2015, Florida experienced an increase in oxycodone-caused deaths, the first in six years [35]. 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 [37; 38]. In May 2017, 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 [38]. As part of this order, the State Health Officer has issued a standing order for opioid antagonists to ensure emergency responders have access [38]. The order has been extended several times and, as of August 2021, it is still in place.

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. Analyses of data from 2013–2015 indicate sharp increases in overdose fatalities in Florida linked to counterfeit alprazolam, oxycodone, and hydrocodone tablets that contained fentanyl [39]. 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 [40].

In Florida, fatalities with benzodiazepines present peaked in 2010 with 6,188, falling to 2,182 in 2020 (38% were alprazolam) [41]. Other primary contributors to opioid analgesic-related fatalities include alcohol and prescribed methadone [30; 42].

In addition to the executive order issued in 2017, several new state laws were passed in 2018 to impose additional legal requirements on controlled substance prescribers [43]. 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 [44]. In addition, the CDC further updated guidance against the misapplication of this guideline in 2019, noting that some policies and practices attributed to the guideline were inconsistent with the recommendations [45]. 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 [46; 47; 48; 49].

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 [50]. 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 [51].

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 [44; 52]. Initial treatment should always be considered individually determined and as a trial of therapy, not a definitive course of treatment [53].

### 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 [44]. 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 [54]:

- 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 [55; 56; 57].

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; these guidelines are forthcoming [54].

### 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 [44; 58].

  

| RISK STRATIFICATION FOR PATIENTS PRESCRIBED OPIOIDS |
|---|
| **Low Risk** |
| No or well-defined and controlled personal or family history of alcohol/substance use disorder<br>No or minimal co-occurring psychiatric disorders or medical comorbidities<br>Age 45 years or older<br>High levels of pain acceptance and active coping strategies<br>High motivation and willingness to participate in multimodal therapy, attempting to function at normal levels |
| **Medium Risk** |
| Moderate concomitant psychiatric disorders, well controlled by therapy<br>Moderate coexisting medical disorders well-controlled by medical therapy and not affected by chronic opioid therapy (e.g., central sleep apnea)<br>History of personal or family alcoholism/substance abuse/addiction<br>Willing to participate in multimodal therapy, attempting to function in normal daily life<br>Pain involving more than three regions of the body |
| **High Risk** |
| Widespread pain without objective signs and symptoms<br>Pain involving more than three regions of the body<br>Aberrant drug-related behavior<br>History of alcoholism or drug misuse, abuse, addiction, diversion, dependency, tolerance, or hyperalgesia<br>Major psychologic disorders<br>Age younger than 45 years<br>Unwilling to participate in multimodal therapy, not functioning close to a near normal lifestyle |
| *Source: [1; 59; 60; 61]* *Table 1* |

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 [51].

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 [62].

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 a treatment/recovery program or other arrangements 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 [44; 63].

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 [64].

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 19, 2021.)

**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 [65; 66].

### 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 [67; 68].

### Screening Instrument or Substance Abuse Potential (SISAP)

The Screening Instrument or Substance Abuse Potential (SISAP) tool is a self-administered, five-item questionnaire addressing history developed to predict the risk of opioid misuse. The SISAP is used to identify patients with a history of alcohol/substance abuse and improve pain management by facilitating focus on the appropriate use of opioid analgesics and therapeutic outcomes in the majority of patients who are not at risk of opioid abuse, while carefully monitoring those who may be at greater risk [69].

### 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 [70].

### 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 [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; 44]. 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) [54].

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 nonopioid and immediate-release opioids over long-acting/extended-release opioids. Taper opioid dose when no longer needed [63].

  

**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 of methods, 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***

Nonopioid 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 nonopioid analgesics; that is, there is a dose beyond which there is no further analgesic effect. In addition, many side effects of nonopioids 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.

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

**PERIODIC REVIEW AND MONITORING**

When implementing a chronic pain treatment plan that involves the use of opioids, the patient should be frequently reassessed for changes in pain origin, health, and function [1]. This can include input from family members and/or the state PDMP. During the initiation phase and during any changes to the dosage or agent used, patient contact should be increased. At every visit, chronic opioid response may be monitored according to the "5 A's" [1; 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 or 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. Family members can observe whether a patient is losing control of his or her life or becoming less functional or more depressed during the course of opioid therapy. They can also provide input regarding positive or negative changes in patient function, attitude, and level of comfort. The following questions can be asked of family members or a spouse to help clarify whether the patient's response to opioid therapy is favorable or unfavorable [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 [77]:

- 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 [58]. Sample questions include: In the past 30 days, how often have you had to take more of your medication than prescribed? In the past 30 days, how much of your time was spent thinking about opioid medications (e.g., having enough, taking them, dosing schedule)?

**Pain Assessment and Documentation Tool (PADT)**

Guidelines by the CDC, the Federation of State Medical Boards (FSMB), and the Joint Commission stress the importance of documentation from both a healthcare quality and medicolegal perspective. Research has found widespread deficits in chart notes and progress documentation 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. However, the potential aberrant drug-related behavior section must be completed by the physician based on his or her observations of the patient [80].

**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].

  

| PATIENT RISK LEVEL AND FREQUENCY OF MONITORING | | | |
|---|---|---|---|
| **Monitoring Tool** | **Patient Risk Level** | | |
| | **Low** | **Medium** | **High** |
| Urine drug test | Every one to two years | Every 6 to 12 months | Every three to six months |
| State prescription drug monitoring program | Twice per year | Three times per year | Four times per year |
| *Source: [81]* | | | *Table 2* |

**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 [44]. However, this recommendation was based on low-quality evidence that indicates little confidence in the effect estimate.

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 [63]. A copy of this form may be accessed online at https://www.accessdata.fda.gov/drugsatfda_docs/rems/ERLA_opioids_2016-04-26_Patient_Counseling_Document.pdf [83].

When prescribing opioids, clinicians should provide patients with the following information [63]:

- 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 [84]. 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 [85]. 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]. The FDA provides a free toolkit of materials (e.g., social media images, fact sheets, posters) to raise awareness of the serious dangers of keeping unused opioid pain medicines in the home and with information about safe disposal of these medicines. The Remove the Risk Outreach toolkit is updated regularly and can be found at https://www.fda.gov/drugs/ensuring-safe-use-medicine/safe-opioid-disposal-remove-risk-outreach-toolkit [86]. 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.

The American College of Preventive Medicine has established best practices to avoid diversion of unused drugs and educate patients regarding drug disposal [84]:

- 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; 44].

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].

## 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 [87]. Since the first community-based opioid overdose prevention program began distributing naloxone in 1996, more than 10,000 overdoses have been reversed [87].

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 [88]. Emergency responders include (but are not limited to) law enforcement officers, paramedics, and emergency medical technicians [88]. As noted, there is a statewide standing order for naloxone for all emergency responders in Florida [38].

### 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 [89].

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 [90]. In 2014, the FDA approved naloxone as an autoinjector dosage form for home use by family members or caregivers, and in 2015, the agency approved intranasal naloxone after a fast-track designation and priority review. Intranasal naloxone is indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression [91; 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. The intranasal formulation is 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 [95].

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 [96]. 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 [97]. This law establishes the standards for controlled substance prescribing, including reporting system requirements, for prescribers and pharmacists in Florida. As of 2021, the Florida schedule of controlled substances aligns with the DEA schedule [43].

### 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].

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 [99]. This is mandated even for existing patients and should be done each time a controlled substance is prescribed or dispensed [43]. 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 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 [99]. This should be repeated each time the substance is dispensed. This reporting requirement is waived in certain circumstances, including for [99]:

- 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 2019 National Survey on Drug Use and Health asked non-medical users of prescription opioids how they obtained their most recently used drugs [100]. Among persons 12 years of age or older, 38.6% obtained their prescription opioids from a friend or relative for free, 34.7% got them through a prescription from one doctor (vs. 17.3% in 2009–2010), 9.5% bought them from a friend or relative, and 3.2% took them from a friend or relative without asking [100]. Less frequent sources included a drug dealer or other stranger (6.5%); multiple doctors (2.0%); and theft from a doctor's office, clinic, hospital, or pharmacy (0.8%) (vs. 0.2% in 2009–2010) [100].

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 [101]. 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 [102].

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; 103; 104]:

- 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; 103; 104]:

- 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" [84]. In addition, patients should be aware of the many options available to treat chronic pain aside from opioids. To prevent theft, patients should be advised to keep medications in a private place and to refrain from telling others about the medications being used.

Communication among providers and pharmacies can help to avoid inappropriate attainment of prescription drugs through "doctor shopping." Prescribers should keep complete and up-to-date records for all controlled substance prescribing. When possible, electronic medical records should be integrated between pharmacies, hospitals, and managed care organizations [84]. 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 [84].

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 [84; 105]. 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 [105].

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, "Physicians have an obligation to support continuity of care for their patients. 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" [106]. The notice of termination should be sent in writing, should specifically note the causes for the termination, and should give a period of time prior to termination, usually 30 days [107]. 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 [108].

## 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 - #45121 STRATEGIES FOR APPROPRIATE OPIOID PRESCRIBING: 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 August 31, 2024.***

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) *2011.*
   B) *2001.*
   C) *1990.*
   D) *1981.*

3. **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. **The U.S. Food and Drug Administration recommends that unused OxyContin tablets be disposed of by**
   A) *burning.*
   B) *flushing down the toilet.*
   C) *throwing in the garbage in a sealed container.*
   D) *sharing with a friend or relative with chronic pain.*

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 dispense controlled substances are required to report the action to the Electronic Florida Online Reporting of Controlled Substances Evaluation (E-FORCSE) within**
   A) *2 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.***

  

# Frontotemporal Dementia

**In addition to receiving *AMA PRA Category 1 Credit*™, physicians participating in Maintenance of Certification will receive the following points appropriate to their certifying board: 2 ABIM MOC Points, 2 ABS MOC Points.**

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

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

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

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

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

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

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

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

### *Division Planner*
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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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.

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## INTRODUCTION

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

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

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

## EPIDEMIOLOGY OF FTD

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

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

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

## PATHOGENESIS AND PATHOPHYSIOLOGY OF FTD

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

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

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

## CLINICAL PRESENTATION

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

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

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

palsy (PSP), corticobasal syndrome (CBS), or motor neuron disease (MND). Some patients may present with symptoms that overlap the different subtypes of FTD or may develop symptoms of other subtypes of FTD as the disease evolves. As more is learned about FTD, the terminology and classification of the subtypes may be revised.

## BEHAVIORAL PRESENTATION

### Behavioral Variant FTD

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

## LANGUAGE PRESENTATION

### Nonfluent/Agrammatic Variant PPA

Nonfluent/agrammatic variant PPA, also referred to as progressive non-fluent aphasia (PNFA), accounts for about 25% of all FTD cases and involves problems with language expression [12]. People with nfvPPA have difficulty producing speech but retain the meaning of words and know what they want to say. As a result, speech may become hesitant, slow, and labored. Speech patterns may be "agrammatic" or "telegraphic," meaning that only the most important content words are used, without connecting words. For example, a patient might say "Tuesday...hospital...sister." Patients with nfvPPA have difficulty talking on the telephone and tend to talk progressively less. Eventually, some may become mute. While in the early stages, these patients continue to understand the speech of others, but this comprehension is eventually lost also. Reading and writing skills are better preserved than speech, although these abilities are also eventually lost. As the disease progresses, patients may develop behavioral symptoms. Some individuals with nfvPPA may develop extrapyramidal symptoms of rigidity and tremors, as seen in CBS and PSP.

  

### Semantic Variant PPA

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

### Logopenic Variant PPA

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

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

## FTD OVERLAP WITH MOVEMENT DISORDERS

### Progressive Supranuclear Palsy

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

### Corticobasal Syndrome

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

### FTD with Motor Neuron Disease

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

## CLINICAL DIAGNOSIS OF FTD

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

The clinical diagnosis of FTD is based on the clinical history, family history, neurologic examination, neuropsychologic evaluation, and neuroimaging. Other tests may also be performed for differential diagnosis. The diagnostic process may take time, and the diagnosis may change as more tests are done or as new symptoms appear.

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

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

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

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

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

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

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

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

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

  

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

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

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

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

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

## GENETICS AND FTD

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

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

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

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

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

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

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

Clinical genetic testing is available for the *MAPT*, *GRN*, and *C9orf72* genetic mutations causing hereditary FTD, as well as some of the other very rare genetic mutations. Genetic testing may be ordered after informed consent and clear discussion of the implications with the patient and his/her family. For patients with FTD, identification of a genetic mutation confirms the diagnosis of FTD and provides information about risk to other family members. Each of the patient's siblings and each of the patient's children would be at 50/50 risk for having inherited the genetic mutation causing FTD. If a genetic mutation causing FTD is identified, other at-risk family members may be tested.

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

## MANAGEMENT OF FTD

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

EVIDENCE-BASED PRACTICE RECOMMENDATION

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

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

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

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

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

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

  

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

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

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

## CAREGIVER SUPPORT

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

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

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

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

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

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

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

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

## PROGRESSION OF FTD

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

## RESEARCH RELATED TO FTD

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

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

## CASE STUDY

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

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

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

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

  

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

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

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

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

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

## CONCLUSION

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

## RESOURCES

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

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

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

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

## COURSE TEST - #96102 FRONTOTEMPORAL DEMENTIA

*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 October 31, 2024.***

**1. The age of onset for frontotemporal dementia (FTD) is typically**
- A) *20 to 30 years.*
- B) *30 to 45 years.*
- C) *45 to 64 years.*
- D) *65 years or older.*

**2. Which areas of the brain are typically atrophied in patients with FTD?**
- A) *Substantia nigra and pons*
- B) *Occipital and parietal lobes*
- C) *Hippocampus and thalamus*
- D) *Frontal and anterior temporal lobes*

**3. The most common presentation of FTD is**
- A) *behavioral variant FTD.*
- B) *corticobasal degeneration.*
- C) *semantic variant primary progressive aphasia.*
- D) *logopenic variant primary progressive aphasia.*

**4. Which of the following personality traits or behaviors is typically seen with behavioral variant FTD (bvFTD)?**
- A) *Empathy*
- B) *Sociability*
- C) *Inhibitions*
- D) *Compulsive behaviors*

**5. A person diagnosed with nonfluent/agrammatic variant primary progressive aphasia would have difficulty**
- A) *producing speech.*
- B) *recognizing a familiar face.*
- C) *remembering the correct word.*
- D) *understanding the meaning of a word.*

**6. Which of the following best describes the differences between the early symptoms of FTD and Alzheimer disease (AD)?**
- A) *Age of onset is generally earlier in AD than FTD.*
- B) *Memory decline is generally the first symptom of AD, whereas behavior, language, and/or movement decline are generally the first symptoms of FTD.*
- C) *Problems with gait, balance, rigidity, apraxia, or muscle weakness occur frequently in early AD, whereas movement problems are rare in early FTD.*
- D) *Language problems in FTD involve word-finding, whereas language problems in AD involve speech production, understanding word meaning, and recognizing familiar objects.*

**7. If a parent carries a genetic mutation in the *MAPT* gene causing FTD, what is the risk to his/her child of inheriting the same genetic mutation?**
- A) *Less than 1%*
- B) *25%*
- C) *50%*
- D) *More than 99%*

**8. Which of the following medications has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of FTD?**
- A) *Donepezil*
- B) *Trazadone*
- C) *Olanzapine*
- D) *No medication has been approved by the FDA for the treatment of FTD.*

  

**9. In developing a plan to manage symptoms in a patient with bvFTD, it is important to consider which of the following?**

*A) People with bvFTD typically have anorexia, so high-calorie diets are encouraged.*

*B) People with bvFTD typically respond negatively to physical activity, so exercise programs should be avoided.*

*C) People with bvFTD typically have apathy and problems maintaining good hygiene, so increasing supervision of hygiene and grooming is needed.*

*D) People with bvFTD typically maintain socially appropriate behavior around children, so behavior supervision is not needed when children are present.*

**10. All of the following are goals of current research on FTD, EXCEPT:**

*A) Improving diagnosis*

*B) Stopping the infectious spread of the disease*

*C) Developing therapies to treat, cure, and prevent the disease*

*D) Identifying causes and risk factors, both genetic and environmental*

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.***

# Psychedelic Medicine and Interventional Psychiatry

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

### *Audience*

The course is designed for all members of the interprofessional team, including physicians, physician assistants, nurses, and mental health professionals, involved in caring for patients with mental disorders resistant to traditional treatment approaches.

### *Course Objective*

The purpose of this course is to provide medical and mental health professionals with the knowledge and skills necessary to effectively treat mental disorders using emerging psychedelic and interventional techniques.

### *Learning Objectives*

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

1. Outline factors that have contributed to the rise in interest in psychedelic and interventional psychiatry.
2. Define terms related to the discussion of psychedelic and interventional psychiatry.
3. Discuss the history of psychedelics in medical care.
4. Evaluate factors that may impact the provision of psychedelic or interventional psychiatry techniques, including stigma, setting, and culture.
5. Outline the role of psilocybin and ketamine in psychiatric care.
6. Describe how MDMA and ibogaine may impact mental health.
7. Review the clinical effects of kratom, LSD, and mescaline.
8. Discuss the potential clinical role of nitrous oxide, ayahuasca, and dimethyltryptamine (DMT).
9. Describe how psychedelics may be incorporated into the treatment of mental health disorders, including treatment-resistant depression, post-traumatic stress disorder, and substance use disorders.
10. Identify interventional approaches that may be used in the treatment of mental health disorders.

### *Faculty*

**Mark S. Gold, MD, DFASAM, DLFAPA**, is a teacher of the year, translational researcher, author, mentor, and inventor best known for his work on the brain systems underlying the effects of opiate drugs, cocaine, and food. Dr. Gold was a Professor, Eminent Scholar, Distinguished Professor, Distinguished Alumni Professor, Chairman, and Emeritus Eminent Scholar during his 25 years at the University of Florida. He was a Founding Director of the McKnight Brain Institute and a pioneering neuroscience-addiction researcher funded by the NIH-NIDA-Pharma, whose work helped to de-stigmatize addictions and mainstream addiction education and treatment. He also developed and taught courses and training programs at the University of Florida for undergraduates and medical students. (A complete biography appears at the end of this course.)

### *Faculty Disclosure*

Contributing faculty, Mark S. Gold, MD, DFASAM, DLFAPA, 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*

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

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Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 10 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit. Completion of this course constitutes permission to share the completion data with ACCME.

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

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Through an agreement between the Accreditation Council for Continuing Medical Education and the Royal College of Physicians and Surgeons of Canada, medical practitioners participating in the Royal College MOC Program may record completion of accredited activities registered under the ACCME's "CME in Support of MOC" program in Section 3 of the Royal College's MOC Program.

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## INTRODUCTION

A new and intense interest in psychedelic drugs and interventional medicine is occurring now in the United States and worldwide, as scientists are exploring and discovering innovative ways to treat challenging psychiatric problems, including treatment-resistant depression, suicidal major depressive disorder, post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), and substance use disorders, as well as multiple other psychiatric problems that have largely been impervious to traditional treatment. Psychedelic medicine refers to the use of drugs that are hallucinogenic and/or anesthetic and that have a unique action on the brain. These approaches may be used only in research situations or may be in current and active use as treatments. In contrast, interventional psychiatry refers to the use of brain-stimulating therapies to treat severe psychiatric disorders. These therapies include electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), and deep brain stimulation (DBS). As with psychedelic medicine, interventional medicine may be used to provide relief for patients with multiple major and previously unremitting severe psychiatric disorders, although there is still much to learn about these therapies. This course will provide an overview of both of these forms of treatment, with an emphasis on psychedelic medicine.

Today, psychedelics like *N*, *N*-dimethyltryptamine (DMT), psilocybin, 3,4-methylenedioxymethamphetamine (MDMA), and lysergic acid diethylamide (LSD) are being explored to treat various psychiatric disorders. Trials of these drugs are in different stages, and the timeline for U.S. Food and Drug Administration (FDA) approval is not always obvious. While ketamine was approved in 2020, most experts believe the first psychedelic approval will come in 2024, likely for PTSD rather than treatment-resistant depression, even though treatment with psilocybin was found to relieve symptoms of major depressive disorder for at least one year for some patients in a 2022 Johns Hopkins study [1]. The safety and efficacy of MDMA-assisted therapy is currently under Phase 3 investigation, but concerns remain regarding efficacy and potential adverse effects. As of 2022, the Multidisciplinary Association of Psychedelic Studies (MAPS) is sponsoring MAPP2, the second of two Phase 3 trials to support FDA approval of MDMA as a breakthrough-designated therapy for the estimated 9 million adults in the United States who experience PTSD each year. In MAPS's first Phase 3 study, 88% of participants with severe PTSD experienced a clinically significant reduction in PTSD diagnostic scores two months after their third session of MDMA-assisted therapy, compared with 60% of placebo participants. Additionally, 67% of participants in the MDMA group no longer met the criteria for PTSD two months after the sessions, compared with 32% of participants in the placebo group [2].

When effective, psychedelic medicine is analogous to a "resetting" of the brain. It is somewhat like when a computer runs awry, and nothing of many actions that the user tries improves the situation. In frustration, the user shuts off the machine, but when the device is turned back on, everything works perfectly. The machine has reset itself. Similarly, psychedelic drugs, when effective, may aid the brain in a sort of resetting. Depending on the individual and the drug, the person may find they have marked improvements in symptoms of depression, PTSD, addiction, or other severe psychiatric problem.

As a result of today's research renaissance on psychedelic drugs, there is a new era of hope for people with major psychiatric disorders who have been largely unresponsive to traditional treatments.

One concern about psychedelic medicine is that many of the drugs may induce hallucinations, even in the low doses used for depression. Mental health professionals who prescribe or administer the drugs will need to ensure patients are monitored adequately. In some cases, the person receiving the drug is hospitalized, but in others, the drug is administered and changes observed in an office setting.

Ketamine's efficacy and protocols to ensure safety have resulted in thousands of patients being treated and reporting excellent responses for treatment-resistant depression. However, the ideal drug would provide the benefits without the hallucinatory side effects. In one unique experiment with mice, researchers effectively blocked 5-HT2A, the serotonin-detecting receptor, and this action appeared to stop mice being administered psilocybin from hallucinating ("tripping"). The antidepressant effects were unaltered in this study, as evidenced by the mice resuming consumption of sugar water, an act they had abandoned while depressed [5]. This is an area of great interest, with the potential that the hallucinations induced by psychedelic drugs could be blocked and increase the acceptability of these agents in the general treatment of depression.

Of course, there are many who believe that the psychedelic trip itself, hallucinations and all, is the crucial experience that allows people to experience psychic relief. These individuals believe that eliminating the crucial experience of hallucination would essentially block the full efficacy of the drug. This issue is likely to continue to be discussed and debated as the science advances.

Psychedelic drugs are often divided into two categories: classic and non-classic or dissociative. The classic psychedelics are usually derived from naturally occurring compounds and include such drugs as psilocybin, LSD, and DMT, an active component of ayahuasca, an increasingly popular sacramental drink originating from South America. The dissociative psychedelics are typically newer analogs and include ketamine, phencyclidine (PCP), MDMA, mescaline, *Salvia divinorum*, and dextromethorphan (DXM). While considered drugs of abuse,

most agents being tested in psychedelic medicine clinical trials are not self-administered by laboratory animals, the usual test for abuse and dependence liability. If anything, hallucinogens tend to lose their ability to produce changes in the person over time and with regular use. These drugs are all variations on tryptamine, and while they may increase dopamine, they tend to do this through an indirect mechanism.

In their 1979 publication, Grinspoon, Grinspoon, and Bakalar define a classic psychedelic drug as [6]:

> A drug which, without causing physical addiction, craving, major physiological disturbances, delirium, disorientation, or amnesia, more or less reliably produces thought, mood, and perceptual changes otherwise rarely experienced except in dreams, contemplative and religious exaltation, flashes of vivid involuntary memory, and acute psychosis.

While the classic versus non-classic designation is of interest to researchers, it is likely not an important distinction for prescribers or patients.

## THE IMPORTANCE OF PSYCHEDELIC AND INTERVENTIONAL MEDICINE

There are multiple reasons health and mental health professionals would benefit from education about both psychedelic and interventional medicine. Psychedelic medicine is a multi-billion-dollar industry and is rapidly growing. It is likely that many healthcare professionals will become involved with these approaches as they enter more widespread use.

Many people in the United States suffer from severe depression, and suicide is a public health problem. In 2020, 21,570 people in the United States died from homicide, a significant increase from the number just one year earlier [7]. However, it did not come close to the suicide rate. In 2020, 45,855 people in the United States died from suicide. The annual U.S. suicide rate increased 30% between 2000 and 2020 [7]. As such, depression and suicide are major health problems in the United States today, and approaches to reverse depression rapidly and safely are greatly needed.

It is also important to consider the frustration of many patients with treatment-resistant depression and other disorders, many of whom have turned to cannabis to obtain relief. The majority of states have enacted laws approving medical marijuana, although its efficacy in the treatment of PTSD, depression, and other psychiatric disorders is often lacking [8]. Patients are clearly open to seeking help wherever it may be, whether evidence and healthcare professionals support the approaches. As such, it is vital that clinicians be aware of and knowledgeable regarding novel uses of psychedelic drugs and interventional psychiatry to best serve their patients.

Academic experts, universities, and medical groups continue to research psychedelic medicine, with exciting major breakthroughs in the treatment of depression/anxiety at the end of life and providing relief to patients with treatment-resistant depression, PTSD, and other disorders that most psychiatrists consider difficult to treat. This research will be detailed later in this course.

### TREATMENT-RESISTANT DEPRESSION AND THE RISK OF SUICIDE

As noted, the suicide rate in the United States is more than twice as high as the homicide rate [7]. In 2019, suicide was the second leading cause of death for people 10 to 34 years of age and the tenth leading cause of death across all age groups (***Table 1***). Overall, suicide accounts for 1.7% of all deaths in the United States. Although official national statistics are not compiled on attempted suicide (i.e., nonfatal actions), it is estimated that 1.2 million adults (18 years of age and older) attempted suicide in 2020 [9]. Overall, there are roughly 25 attempts for every death by suicide; this ratio changes to 100 to 200:1 for the young and 4:1 for the elderly [9].

People with depression may experience suicidal ideation and behaviors, which can subsequently lead to suicide completions. As illustrated by ***Figure 1***, in 2020, adults 18 to 25 years of age had the highest risk for a major depressive episode, followed by those 25 to 49 years of age. In addition, individuals of two or more races had the highest risk for depression (15.9%), followed by White individuals (9.5%).

Suicidal behaviors are a major problem in the United States, as depicted in the converging circles shown in ***Figure 2***. This figure demonstrates that 12.2 million adults seriously considered suicide in 2020, represented by the outer circle, while 3.2 million adults made suicide plans, and 1.2 million adults attempted suicide. Of those adults who attempted suicide in 2020, 920,000 had made a suicide plan; 285,000 adults had made no such plan prior to the attempt [10; 12].

Clearly, action is needed to help address depression and suicide in the United States, and psychedelic and interventional medicine may have a role.

### POOR RESPONSE TO ANTIDEPRESSANTS

When they were first introduced, the monoamine oxide (MAO) inhibitors and tricyclic antidepressants were perceived as wonder drugs for depression. However, MAO inhibitors require strict dietary constraints, and both drug classes are associated with multiple troubling side effects. In contrast, when selective serotonin reuptake inhibitors (SSRIs) were introduced, they were much easier to prescribe and expanded treatment approaches to include primary care. Unfortunately, for many patients, SSRIs did not help as much as expected—or indeed at all, in some cases. Today, it is clear that non- or under-response to pharmacotherapy for major depression is far more common

| LEADING CAUSE OF DEATH IN THE UNITED STATES FOR SELECT AGE GROUPS, 2019 | | | | | | | |
|---|---|---|---|---|---|---|---|
| Rank | Age (in Years) | | | | | | |
| | 10–14 | 15–24 | 25–34 | 35–44 | 45–54 | 55–64 | All Ages |
| 1 | Unintentional injury (778) | Unintentional injury (11,755) | Unintentional injury (24,516) | Unintentional injury (24,070) | Malignant neoplasms (35,587) | Malignant neoplasms (111,765) | Heart disease (659,041) |
| 2 | Suicide (534) | Suicide (5,954) | Suicide (8,059) | Malignant neoplasms (10,695) | Heart disease (31,138) | Heart disease (80,837) | Malignant neoplasms (599,601) |
| 3 | Malignant neoplasms (404) | Homicide (4,774) | Homicide (5,341) | Heart disease (10,499) | Unintentional injury (23,359) | Unintentional injury (24,892) | Unintentional injury (173,040) |
| 4 | Homicide (191) | Malignant neoplasms (1,388) | Malignant neoplasms (3,577) | Suicide (7,525) | Liver disease (8,098) | CLRD (18,743) | CLRD (156,979) |
| 5 | Congenital anomalies (189) | Heart disease (872) | Heart disease (3,495) | Homicide (3,446) | Suicide (8,012) | Diabetes (15,508) | Stroke (150,005) |
| 6 | Heart disease (87) | Congenital anomalies (390) | Liver disease (1,112) | Liver disease (3,417) | Diabetes (6,348) | Liver disease (14,385) | Alzheimer disease (121,499) |
| 7 | CLRD (81) | Diabetes (248) | Diabetes (887) | Diabetes (2,228) | Stroke (5,153) | Stroke (12,931) | Diabetes (87,647) |
| 8 | Influenza/ pneumonia (71) | Influenza/ pneumonia (175) | Stroke (585) | Stroke (1,741) | CLRD (3,592) | Suicide (8,238) | Nephritis (51,565) |
| 9 | Stroke (48) | CLRD (168) | Complicated pregnancy (532) | Influenza/ pneumonia (951) | Nephritis (2,269) | Nephritis (5,857) | Influenza/ pneumonia (49,783) |
| 10 | Benign neoplasms (35) | Stroke (158) | HIV (486) | Septicemia (812) | Septicemia (2,176) | Septicemia (5,672) | Suicide (47,511) |

CLRD = chronic lower respiratory disease, HIV = human immunodeficiency disease.

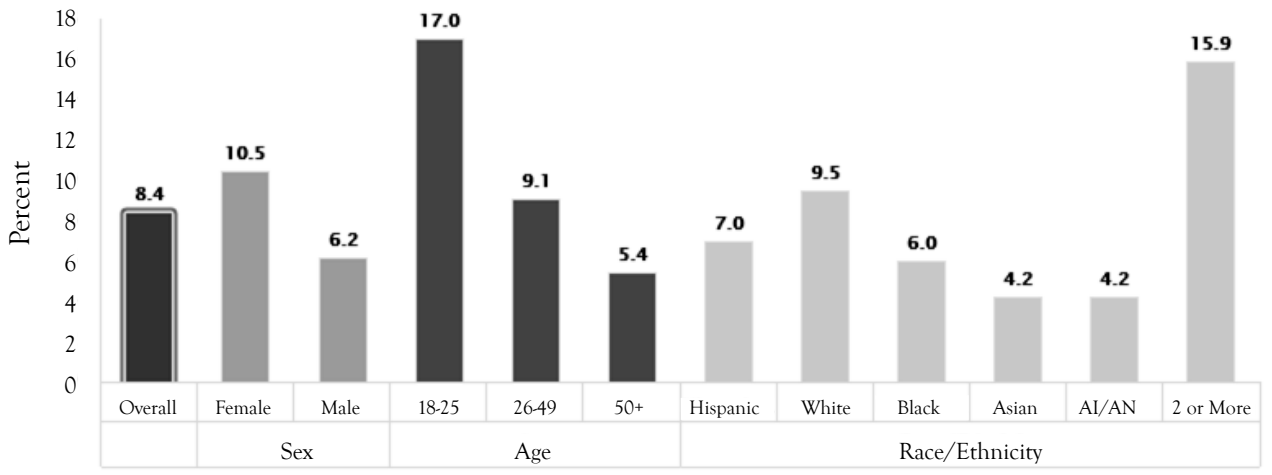
*Source: [10]* *Table 1*

than was realized at the time. For example, researchers have found that antidepressants are ineffective for at least one-third of individuals who take them [2]. Suboptimal responses are also common. Many patients for whom the drugs do not work will recalibrate their expectations and accept the treatment response as the best they can hope to achieve. Treatment discontinuation is common among frustrated patients.

It is also important to note that even when antidepressants actually are efficacious, it usually takes at least three or four weeks for the drug to begin to take effect. Tricyclic antidepressants, MAO inhibitors, SSRIs, and serotonin and norepinephrine reuptake inhibitors (SNRIs) all share this issue of a delayed onset of action. Psychiatrists and neuroscientists have been unable to develop faster-acting medications for depression to date. This means that many people with severe depression could take an antidepressant very faithfully for weeks without any relief. These patients may give up hope and halt treatment or try again with another antidepressant or medication combination.

PAST YEAR PREVALENCE OF MAJOR DEPRESSIVE EPISODE AMONG U.S. ADULTS, 2020

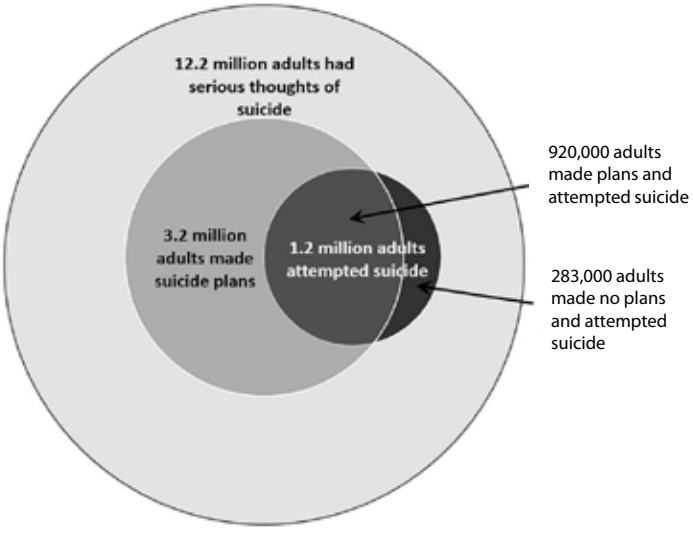



AI/AN = American Indian/Alaska Native

*Source: [11]*

*Figure 1*

SUICIDAL BEHAVIORS IN THE UNITED STATES, 2020




*Source: [10; 12; 14]*

*Figure 2*

As with any pharmacotherapy, antidepressants have many possible adverse effects, including weight gain, anorgasmia, sluggishness, anxiety, insomnia, and suicidal ideation. As such, a patient may experience no improvements in depression symptoms while also developing adverse drug effects. This is not the end of consequences; discontinuation symptoms are also a concern. Antidepressant discontinuation symptoms can be very challenging. For example, abruptly ending fluoxetine can cause nightmares, vomiting, and irritability. In most cases, patients who no longer wish to take an antidepressant should taper off the drug on a defined schedule [3].

To recap, patients may take antidepressants for months without significant improvements in depression symptoms while also experiencing side effects, and when they stop taking these ineffective drugs, they suffer more side effects unless they carefully taper off. In contrast, some psychedelic drugs have the potential to provide relief in a few sessions, with lasting efficacy over months or even years, although further research is needed. This contrast is the main reason that so many mental health professionals and patients are intrigued about the possibilities of psychedelic medicine, particularly for more difficult cases.

It is not clear why antidepressants work for some patients and not for others. Some have hypothesized it may be related to the size and shape of a person's neurons, which can vary considerably [3]. Another possible contributing factor is the similar mechanisms of action among the different classes of antidepressants. These agents increase blood levels of serotonin, dopamine, or norepinephrine. In contrast, some psychedelic drugs, such as ketamine, are *N*-methyl-D-aspartate (NMDA)/glutamate receptor antagonists. This represents a completely different target for antidepressant mechanism of action and also a novel approach to treating depression.

There is also some evidence that ketamine can reverse suicidality or depression after a single dose, which suggests that the drug reverses a neurochemical deficit that is close to the problem. Ketamine and psychedelic drugs are effective at promoting plasticity, reconnections, and healing within the brain, a feat beyond the capabilities of traditional antidepressants or most other drugs. Researchers have found that neuroplastic changes, specifically atrophy of neurons in the prefrontal cortex, are an underlying etiology of depression and other mood disorders. The extent to which these drugs, and ketamine in particular, are able to promote structural and functional plasticity in the prefrontal cortex is believed to underlie the fast-acting antidepressant properties [4]. Other drugs, such as LSD and DMT, may stimulate the formulation of synapses [4]. Psychedelic drugs may also create new connections within the brain, although much more research is needed to understand how and why these drugs may be effective in treating serious psychiatric disorders in some who have heretofore not proven responsive to traditionally effective treatments.

## A GROWING MARKET

Certainly, psychedelic medicine is regarded as a major and burgeoning healthcare market. Data Bridge Market Research has estimated that the market for psychedelic drugs will more than triple, from about $2 billion in 2019 to nearly $7 billion by 2027 [13]. Other estimates are even more favorable; a report from Research and Markets anticipates a market of $10.75 billion in psychedelic drugs by 2027 [13]. In a post-COVID world in which the numbers of people with reported depression have increased by as much as three times, potentially effective treatment options should not be ignored.

It has been estimated that at least 50,000 therapists will be needed by 2031 to provide psychedelic-assisted therapy to patients, and as a result, some organizations have already begun to increase their hiring. The key types of therapies used will be cognitive-behavioral therapy (CBT), acceptance and commitment therapy (ACT), or other types of therapy adapted to psychedelic treatment [15].

The current high interest in psychedelic medicine may stimulate pharmaceutical companies to research and develop novel drug treatments for major psychiatric problems beyond the traditional classes of drugs that solely target serotonin, norepinephrine, and dopamine, which would be yet another positive consequence.

## CONSUMER INTEREST

At the same time that the federal government has somewhat loosened its tight reins on psychedelic medicine and researchers and medical professionals have begun to explore the use of these agents, there has been a dramatic increase in interest among consumers in Schedule I drugs, particularly in cannabis, but also in psilocybin and other psychedelic drugs. As of 2022, 37 states as well as the District of Columbia and four U.S. territories allow the medical use of cannabis ("medical marijuana") [16]. (Note that medical use of cannabis is a bit of a misnomer, as prescribers generally have little or no involvement with patients who take the drug and it has not attained FDA approval for any condition.) In addition, the U.S. House of Representatives passed a bill to decriminalize cannabis use in 2022 [17]. In addition, 18 states, the District of Columbia, and 2 U.S. territories have legalized the recreational use of cannabis for adults [18]. This followed several years of decriminalization at the local and state levels. While cannabis is not considered a psychedelic drug, its shift toward decriminalization and medicinal use is a sign that a similar path may be beginning for other Schedule I drugs with potential psychiatric benefit. Further, in states that allow medical or recreational use of cannabis for adults, the federal government has largely backed away from taking any punitive measures against individuals who use the drug, even though cannabis remains illegal at a federal level.

This movement may already be advancing with psychedelic drugs. This began with the decriminalization of psilocybin in Denver, Colorado, in 2019, followed by Oakland and Santa Cruz, California. In 2021, the city of Cambridge, Massachusetts, passed a law decriminalizing all "entheogenic plants," which includes the drugs ayahuasca, ibogaine, and psilocybin [19]. As of 2022, the largest city to decriminalize psilocybin is Seattle, Washington [19]. In 2020, the state of Oregon approved the use of psilocybin by consumers [20]. Also in 2020, the District of Columbia decriminalized the use of psilocybin mushrooms as well as other substances found in peyote and ayahuasca [20]. Other states are considering taking similar actions. In 2021, Health Canada, the premier health agency in Canada, approved trials of MDMA-assisted therapy for the treatment of PTSD [15]. It is important to note that it can be dangerous for psilocybin and other psychedelic drugs to be used by individuals who do not understand its risks. As popularity and interest in the medical use of these agents increases, clinicians have a responsibility to educate themselves and their patients about the safe and appropriate use of psychedelics.

A major factor in the popularity of psychedelic drugs is frustration resulting from unrelenting depression, anxiety, chronic pain, or other health and mental health conditions. Some patients may have already tried cannabis to address these conditions, with varying levels of success.

### GROWING BODY OF RESEARCH FROM RESPECTED ACADEMIC AND PHYSICIAN LEADERS

Although researchers have historically chosen to avoid or been blocked from researching psychedelics because of bans by the federal government, this has changed in the past few decades. For example, in 2006, Johns Hopkins Medicine began their research on psychedelic medicine, subsequently producing more than 80 peer-reviewed clinical studies by 2020 [21]. A new home for the Center for Psychedelic and Consciousness Research was created in 2020, the first such establishment in the United States [21]. Private donors provided funding to launch the Center, and since its opening, the Center has also received federal funding for research. In addition, Yale, Massachusetts General Hospital/Harvard, and other psychiatric and research excellence centers are studying psychedelic medications as treatment options for serious psychiatric disorders.

In addition, training programs focusing on psychedelic psychiatry are being established (***Table 2***). Johns Hopkins, New York University, and Yale are collaborating to create a psychedelics-psychiatrist program funded by a grant facilitated by Heffter Research Institute [22].

**PSYCHEDELIC PSYCHIATRY TRAINING PROGRAMS**

**Hopkins-Yale-NYU**
https://medicine.yale.edu/news-article/grant-supports-development-of-training-for-psychiatrists-in-psychedelic-medicine

**MAPS**
https://mapspublicbenefit.com/training

**Mount Sinai**
https://icahn.mssm.edu/research/center-psychedelic-psychotherapy-trauma-research/training-education

*Source: Compiled by Author* *Table 2*

## DEFINITIONS

Clear definitions of the concepts related to psychedelic drugs and interventional psychiatry are helpful. The following is a glossary of terms used throughout this course.

**Classic psychedelic**: Refers to older hallucinogenic drugs, such as psilocybin and LSD. These agents are often derived from natural sources.

**Deep brain stimulation**: With the use of implanted electrodes, the brain is stimulated to treat such psychiatric problems as treatment-resistant depression.

**Electroconvulsive therapy (ECT)**: Stimulation of the brain causing a seizure. This therapy is administered under sedation and is used to help patients with severe psychiatric diagnoses.

**Hallucinogen**: Drug that may cause the user to experience visual, auditory, or other types of hallucinations.

**Neuromodulation therapy**: The use of noninvasive or invasive means to stimulate the brain in order to treat serious psychiatric problems.

**Psychedelic medicine**: The use of mind-altering (typically but not always hallucinogenic or dissociative) drugs by mental health professionals to improve or even provide remission from severe psychiatric problems, such as depression, PTSD, anxiety, and substance use disorders.

**Set**: Refers to the patient's mindset. For example, a person who is anxious and fearful is less likely to have a positive experience with psychedelic medicine than a person who has an open and positive outlook.

**Setting**: Refers to the overall ambiance in which psychedelic medicine is administered. A pleasant atmosphere that makes the individual feel safe is best.

**Transcranial magnetic stimulation**: A noninvasive form of therapy that uses large magnets external to the patient to stimulate the brain.

**Vagus nerve stimulation**: Invasive stimulation of the vagus nerve in order to treat serious, treatment-resistant psychiatric diagnoses.

## PONDERING PSYCHEDELICS

More than 50 years have passed since the federal Controlled Substances Act first criminalized the use of psychedelics in the United States in 1970. The initial use (and misuse) of psychedelic drugs in that era was primarily associated with Timothy Leary, a Harvard professor who promoted the nonmedical use of LSD, a practice subsequently adopted by the amorphous "hippie" counterculture movement of the 1960s and 1970s. Dr. Leary was famously noted as advising his followers to "turn on, tune in, and drop out," scandalizing much of the conservative population of the time. Numerous events led to Leary's loss of reputation, academic standing, and position, but his impact during this period was indisputable. In response to this movement, drugs such as LSD, DMT, psilocybin, and mescaline were all placed in the Schedule I drugs category under the Controlled Substances Act 1970 (***Table 3***).

The categorization of psychedelics as Schedule I drugs immediately halted intense scientific research on psychedelics, which had begun in the 1950s. This prohibition on psychedelic drug research significantly delayed advances in medical knowledge on the therapeutic uses of these agents. While much of the focus at that time was on Timothy Leary and the counterculture's recreational LSD use, some researchers had demonstrated beneficial effects with psychedelic medicine in end-of-life care as well as in the treatment of addiction and other severe psychiatric problems [24].

This research did not restart in the United States in any meaningful way until the 21st century. In this new wave of research, researchers in Phase 2 and 3 clinical trials of psychedelic medications have found the possibility of remission in diverse psychiatric populations (including in patients with PTSD, depression, eating disorders, and substance use disorders) as well as reduction in end-of-life anxiety and despair in those with terminal diagnoses [25]. At the same time, researchers have explored the use of older drugs (e.g., nitrous oxide, ketamine) to treat unrelenting psychiatric disorders.

**PSYCHEDELIC DRUG SCHEDULING**

| Drug | Schedule |
|---|---|
| Ayahuasca/DMT | I |
| Ibogaine | I |
| Ketamine | III |
| Kratom | Not scheduled |
| LSD | I |
| Mescaline | I |
| Nitrous oxide | Not scheduled |
| Psilocybin | I |
| MDMA ("Molly," "Ecstasy") | I |

*Source: [23]* *Table 3*

Another interesting avenue of research has been in the field of addiction medicine. There is some evidence that certain psychedelic drugs, particularly psilocybin, may act as a sort of "anti-gateway drug." Years ago, there was a belief that some (or all) drugs were "gateway drugs," leading inevitably to taking other drugs; for example, this perspective holds that people who smoked marijuana would eventually progress to using "harder" drugs, injecting heroin or other opioids. This theory has largely been discredited and devalued. In fact, several studies have indicated that persons who use hallucinogens are less likely to progress to harder drugs. In one study, researchers used data from nearly 250,000 respondents from the National Survey on Drug Use and Health over the period 2015–2019. Respondents were asked about their past use of classic psychedelics, and these results were then compared to their later abuse (or non-use) of opioids. Individuals who had used psilocybin ("magic mushrooms") in the past had a significantly lower rate (30% lower than average) of opioid misuse and abuse later. This finding was not replicated with other psychedelic drugs [26]. An earlier study using National Survey on Drug Use and Health data for the period 2008–2013 found that past use of classic psychedelics decreased the risk for past-year opioid dependence by 27% and of opioid abuse by 40% [27].

Both of these studies relied on individuals reporting on their past use of psychedelic drugs, and there are multiple possible issues with this type of retrospective reporting. But the idea that past use of drugs such as psilocybin could be protective against opioid misuse and dependence in the future is promising, given the ongoing opioid epidemic in the United States.

## A BRIEF HISTORY OF PSYCHEDELICS

It is unclear how long the various psychedelic substances have been used worldwide, but it is safe to say that some have been used for thousands of years in religious and tribal ceremonies. The earliest known written record of the use of psilocybin mushrooms appeared in the Florentine Codex, a manuscript of ethnographic research of Mesoamerica, particularly of Mexico and the Aztecs, compiled between 1529 and 1579. Psilocybin, mescaline, and ayahuasca (a concoction often brewed in a tea and that includes the psychedelic chemical DMT) have all been used in religious ceremonies in indigenous societies in South and Central America for centuries. The hallucinogenic effects of some plants and fungi also have been known by indigenous cultures and were deliberately exploited by humans for thousands of years. Fungi, particularly some types of mushrooms, are the principal source of naturally occurring psychedelics. Historically, the mushroom extract psilocybin has been used as a psychedelic agent for religious and spiritual ceremonies and as a therapeutic option for neuropsychiatric conditions [28].

### Early Days of LSD

Modern pharmaceutical research on psychedelics started in earnest in 1930s Basel, Switzerland, with research chemist Albert Hofmann. Seeking to create a synthetic alkaloid to the ergot fungus, he developed LSD-25 in 1938. The uses of the drug were not immediately obvious, so it sat on a shelf for five years until Hofmann decided to repeat his synthesis of the chemical. Despite his care, Hofmann accidentally contaminated himself with the drug and thereafter experienced highly unusual sensations as well as dizziness. He described his experience as [29]:

> I lay down and sank into a not unpleasant intoxicated-like condition, characterized by an extremely stimulated imagination. In a dreamlike state, with eyes closed (I found the daylight to be unpleasantly glaring), I perceived an uninterrupted stream of fantastic pictures, extraordinary shapes with intense, kaleidoscopic play of colors. After some two hours, this condition faded away.

Hofmann decided to experiment on himself with what he believed to be a very low dose of LSD, but the dose was high enough for him to experience what he perceived to be demonic possession and other lurid sensations. His physician was called and only noted that Hofmann had extremely dilated pupils, with normal blood pressure and vital signs. When Hofmann related his experiences to his colleagues, they were dubious that he had measured correctly, but to be safe, they took even lower doses. Each experienced what were later referred to as psychedelic mind "trips" [29].

In 1947, Sandoz began marketing and distributing LSD, under the brand name Delysid, as a possible psychiatric drug to treat neurosis, alcoholism, criminal behavior, and schizophrenia. In addition, LSD-25 was also used to treat autism and verbal misbehavior [28; 30]. In his book, Hofmann described how LSD helped provide relief to people who were dying of cancer and in severe pain for whom major analgesics were ineffective. He hypothesized that the analgesic effect was not inherent to the drug but was a result of patients dissociating from their bodies such that physical pain no longer affected them [29].

However, early studies on LSD did not always inform patients about the potential risks. For example, in some cases, patients with schizophrenia were given LSD and not told about the possible risk for a psychotic break [31]. Patients at the Addiction Research Center in Lexington, Kentucky, were often given the drug without being told what it was or the possible effects. Researchers who believed in the importance of "set and setting" (the patient's mindset and the setting where the drug was administered) were more likely to inform patients about possible risks and benefits. The 1962 Kefauver-Harris Amendments required that all patients provide informed consent for therapeutic interventions and research participation. Despite this, the "informed consent" of the 1960s was not as comprehensive as informed consent today. Some have posited that the primary goal was to release researchers from legal responsibility rather than to provide ensure the safety of patients and prospective subjects of clinical trials [31].

For about a decade, Hofmann and Sandoz believed that LSD might provide breakthroughs in psychiatry. However, with the major social change of the 1960s, characterized by protests for social change and against the Vietnam War and increasingly liberal attitudes regarding drugs among young people, the focus shifted to recreational rather than medical use of LSD, and in 1965, Sandoz stopped manufacture and marketing of LSD. In 1966, Sandoz gave their remaining supplies to the National Institute of Mental Health [31].

### Early Days of Psilocybin

In 1957, Hofmann received a sample of dried *Psilocybe mexicana* mushrooms from a mycologist in Huautla de Jiménez in Oaxaca, Mexico. The mycologist, R. Gordon Wasson, had received a sample of the mushrooms and information regarding the sacred rituals of the Mazatec people from a curandera to whom he promised secrecy; this promise was obviously not kept, and Wasson's actions resulted in retaliation against the indigenous woman who he betrayed [138]. Hofmann used paper chromatography to separate the various components of whole extracts of mushrooms and ingested each separated fraction. The active fraction was then chemically characterized, crystallized, and named psilocybin. In 1958, Hofmann and his colleagues subsequently elucidated the structure and synthesis of psilocybin and psilocin, a minor component of the extract that is a dephosphorylated form of psilocybin. In the 1960s,

Sandoz Pharmaceuticals began to distribute Indocybin, a psychotherapeutic drug in pill form, containing 2-mg psilocybin. This period also saw research focusing on psilocybin as a probe for brain function and recidivism and as an entheogen used by religious people (divinity students).

During this era, psilocybin, LSD, mescaline, and other psychedelics were used by some individuals with psychiatric diseases, and they were also used extensively by some psychiatrists to treat patients before the drugs were categorized as Schedule I of the U.N. Convention on Drugs in 1967, which preceded the Controlled Substances Act in the United States. Today, the medical value of hallucinogens is being tested in rigorous trials in settings such as Roland Griffith's Johns Hopkins research program. The experts from the psilocybin research group at Johns Hopkins University have described the importance of trained psychedelic therapists and other components of a psychedelic treatment session to optimize patient safety in hallucinogen research [32].

## CONSIDERING PSYCHEDELIC-ASSISTED PSYCHOTHERAPY AS A TREATMENT OPTION

For most mental health professionals, the idea of psychedelic-assisted psychotherapy is a major paradigm shift and leap from current practices of providing pharmacotherapy or psychotherapy to individuals or groups. At the same time, it may represent a new opportunity to combine the talents and skills of therapists with the proven benefits of a psychedelic drug. Combined psychotherapy/pharmacotherapy is the treatment of choice for most patients with mental health disorders, so interprofessional collaboration is a typical (and vital) part of treatment. Psychedelic medicine requires that diverse disciplines collaborate closely and communicate to clearly ensure that the therapy is safely and effectively administered.

### LEGAL AND REGULATORY BARRIERS

Today, the federal government has provided limited permission or even grants to study Schedule I drugs and their possible role in the treatment of patients. Outside of these limited cases, researchers find it difficult to obtain the needed drug for testing purposes. To avoid legal and regulatory issues, a good amount of research is performed outside of the United States.

### "SET" AND "SETTING" IN PSYCHOTHERAPY-ASSISTED PSYCHEDELIC TREATMENT

Since the 1960s, therapists have noted that the response to psychedelic drugs is impacted by the patient's mindset as well as the setting where the psychedelic drug is administered. For example, if the person feels confident that the experience will be a positive one, then this "set" is considered more conducive to a good experience while under the influence of a psychedelic drug compared with when persons are extremely apprehensive and fearful beforehand. By extension, if patients are in an office setting with a therapist or other practitioner with whom they feel safe, the outcome is generally better than in those who feel unsafe. Research has shown a better outcome with patients receiving psychedelics in a therapeutic setting versus receiving the drug while undergoing a positron emission tomography (PET) scan [33]. These researchers stated [33]:

> The finding that the PET environment was strongly associated with anxious reactions could be partially explained by the perceived atmosphere. Whereas non-PET experiments were mostly conducted in laboratory rooms that were furnished in an aesthetically pleasing way, the environment at the PET center was much more clinical and "antiseptic" (i.e., lots of technical equipment, white walls, personnel in white lab coats). Our results are therefore in support of current safety guidelines, which recommend avoiding "cold" and overly clinical environments in human hallucinogen research in order to reduce the risk of anxious reactions.

Another element of setting, and one that is also used to enhance set, is the use of music while the patient undergoes therapy with psychedelic medicine. Johns Hopkins has developed a "psilocybin playlist" lasting nearly eight hours that is used for patients who are undergoing treatment with psilocybin [34].

In many cases, psychedelic therapy is administered after a therapeutic session. Psychotherapy is often also provided during the course of the drug's effects and at integration sessions that occur after the drug was given to help the patient to give meaning and context for the experience [35]. This provision of multiple hours of psychotherapy over a short period of time can translate to higher costs. This scenario might be less appealing to insurance carriers than traditional therapies (e.g., antidepressants or other drugs), but this is yet to be seen.

It should also be noted that in some areas, there are clear manualized approaches to treating patients that carefully consider both set and setting; this is particularly the case for MDMA in the treatment of PTSD. However, these approaches are yet to be developed for most other psychedelic drugs. Again, this field offers burgeoning opportunities for psychiatrists, psychologists, primary care providers, and other mental health practitioners.

### ADVISING PATIENTS CONSIDERING PSYCHEDELIC MEDICINE

Some patients will approach their primary care providers to discuss the possibility of seeking care at a ketamine or MDMA (or other) clinic. It is important not to dismiss these treatment options out of hand. Instead, it may be best to ask the patients the following questions to help assess if the option would be helpful and if the facility is set up to provide optimal care:

- Who is the expert or experts running this clinic? What experience(s) make this person or team experts? What outcome data are provided?
- Does the patient have a severe and intractable diagnosis, such as treatment-resistant depression, substance use disorder, or PTSD? If not, then conventional medicine is still best.
- Does the clinic ensure professional observation after the drug is administered? This is always advisable in case the patient experiences adverse events.
- How soon after a drug is administered are patients discharged from the facility? Minimal times (e.g., 15 minutes) are not long enough to ensure safety.
- Does the facility offer psychotherapy before, during, and after the drug is administered? Combining psychotherapy with psychedelic medicine is the proven best practice.
- Is there a required follow-up?
- Are the costs for treatments clearly delineated? If not, patients should request, in writing, an estimate of total costs. Psychedelic medicine is likely not covered by health insurance and may be costly. Also, the cost may fluctuate significantly from one clinic to another.
- Has the patient experienced a psychotic break in the past or does the patient have first-degree relatives with a history of psychosis? Psychedelics have the potential to trigger an underlying predisposition for psychosis, although it can be temporary. Still, even a short-term psychotic break is a terrifying experience.

### ADDRESSING STIGMA

For many people, including some clinicians, the phrase "psychedelic medicine" evokes images of free love, 1960s counterculture, and recreational intoxication. In reality, these therapies typically look much more pedestrian, consisting of a patient sitting or lying on a couch while a clinician guides the person through the experience in order to treat their severe psychiatric disorder. Although many of the drugs described in this course can and do induce hallucinations, subjects have reported that these experiences were integral and allowed them to resolve psychiatric issues that have been resistant to traditional treatments and that have significant impact on their lives. If further studies continue to bear these findings out, it would be unwise to ignore the benefits that may accrue.

## EMERGING PSYCHEDELIC TREATMENTS

The key psychedelic drugs actively being researched and/or currently in use today include psilocybin, ketamine, MDMA, ibogaine, kratom, LSD, mescaline, and ayahuasca (***Table 4***). In addition, nitrous oxide, a gas used for many years by dentists as both an anesthesia and analgesic for patients undergoing painful procedures, has also been found effective as a treatment for some psychiatric disorders.

### PSILOCYBIN

Beginning in the 2010s, psilocybin has been undergoing an era of increased research attention, and this compound remains under active investigation. Psilocybin occurs in nature in hundreds of species of mushrooms as 4-phosphoryloxy-*N*,*N*-dimethyltryptamine. However, when used by researchers, the drug is nearly always a chemically synthesized compound to maintain a standard dosage as well as the purity of the drug. In 2020, COMPASS Pathways announced that it had gained a patent in the United States for COMP360, its form of synthetically derived psilocybin [15].

According to a 2022 report from the Associated Press, some states, even in conservative areas (e.g., Utah), have approved studying psilocybin as a treatment. This movement has largely been driven by increasing rates of treatment-resistant PTSD among military veterans [36].

Psilocybin was first studied during the 1960s to establish its psychopharmacologic profile; it was found to be active orally at around 10 mg, with more potent effects at higher doses, with a four- to six-hour duration. Psilocybin is rapidly metabolized to psilocin, a full agonist at serotonin 5-HT1A/2A/2C receptors, with 5-HT2A receptor activation directly correlated with human hallucinogenic activity. Time to onset of effect is usually within 20 to 30 minutes of ingestion. As a drug, it is about 20 times stronger than mescaline but much less potent than LSD [37].

In animal studies of the use of psilocybin, a link has been identified between reduced prefrontal mGluR2 function and both impaired executive function and alcohol craving. Psilocybin also restored healthy mGluR2 expression and reduced relapse behavior in mice [38]. Mice and humans do not always respond equivalently, but this finding may explain why psilocybin is effective in treating induced alcoholism in mice and provides an interesting research avenue in the investigation of psilocybin as a treatment for alcohol use disorder in humans, because relapse is a significant problem; even when a patient has abstained from alcohol for years, the underlying craving remains. If this craving could be reduced or altogether eliminated, this could revolutionize substance use disorder treatment.

**MAJOR PSYCHEDELIC RESEARCH CENTERS IN THE UNITED STATES**

**Johns Hopkins Center for Psychedelic and Consciousness Research**
https://hopkinspsychedelic.org

**National Institutes of Health Funding**
https://pubmed.ncbi.nlm.nih.gov/34624734

**Yale University**
https://medicine.yale.edu/psychiatry/education/residency/interest/psychedelic_science_group

**Mount Sinai**
https://www.mountsinai.org/about/newsroom/2021/mount-sinai-health-system-launches-center-for-psychedelic-research

**Stanford University**
https://med.stanford.edu/spsg.html

**University of California, San Francisco**
https://neuroscape.ucsf.edu/psychedelics

**Duke University**
https://dukepsychedelics.org

**University of Texas at Austin**
https://dellmed.utexas.edu/units/center-for-psychedelic-research-and-therapy

**Washington University in St. Louis (WUSTL)**
https://healthymind.wustl.edu/items/washington-universitys-program-in-psychedelic-research

**Harvard/Massachusetts General Hospital**
https://www.massgeneral.org/psychiatry/treatments-and-services/center-for-the-neuroscience-of-psychedelics

*Source: Compiled by Author* *Table 4*

In a study at King's College London, researchers studied the effects of psilocybin on the emotional and cognitive functions in healthy subjects in a Phase 1 randomized double-blind controlled study with 89 subjects (average age: 36.1 years). Subjects were randomized to receive placebo or 10 mg or 25 mg of psilocybin. Therapists were available to the subjects throughout the sessions. Six subjects at a time received the drug. The study showed that there were no short- or long-term adverse effects to the emotional processing or cognitive functioning of the subjects [39]. In this study, 70% of the subjects who received 25-mg psilocybin experienced visual hallucinations, compared with 60% of those who received 10-mg psilocybin and 6.9% of those who received placebo. The second most common treatment-emergent adverse event was illusion, which was experienced by 60% of subjects receiving 25-mg psilocybin and 63.3% of those receiving 10-mg psilocybin; 13.8% of those receiving placebo reported experiencing this effect. Other treatment-emergent adverse events reported more commonly among the treatment groups included mood alteration, headache, fatigue, and euphoric mood, all of which were lower or altogether non-existent in the placebo group. Also absent in the placebo group were auditory and tactile hallucinations [39]. The researchers concluded [39]:

> This study demonstrated the feasibility of one-to-one psychological support from specially trained therapists during [the] simultaneous administration of psilocybin in a supervised clinical setting in healthy volunteers. A single dose of psilocybin 10 mg or 25 mg elicited no serious adverse effects and did not appear to produce any clinically relevant detrimental short- or long-term effects, compared with placebo, in cognitive or social functioning or emotional regulation in this study in health volunteers.

In studies using psilocybin, the most common adverse reactions were found to be headache, nausea, and hypertension, and events were considered to be equivalent to those found with the use of SSRIs [40]. However, it should also be noted that the subjects in psilocybin clinical trials are usually screened for a family history of schizophrenia, major depression with psychotic features, high risk for suicide, and severe personality disorders before inclusion [40].

Another study at Johns Hopkins evaluated the efficacy and safety of psilocybin for the treatment of major depressive disorder. In this randomized study, 24 patients 21 to 75 years of age with moderate-to-severe unipolar depression were randomized to either immediate or delayed treatment. Subjects were administered two doses of psilocybin along with supportive psychotherapy. Researchers found a greater than 50% reduction in depressive symptoms, as measured by the GRID-Hamilton Depression Rating Scale (GRID-HAMD), in the treatment group. Before initiating psilocybin therapy, subjects first received six to eight hours of preparation with trained facilitators. The psilocybin was administered at doses of 20 mg/70 kg and 30 mg/70 kg, about two weeks apart, while subjects were in a comfortable room supervised by two facilitators. There were also follow-up counseling sessions [1]. The mean scores on the GRID-HAMD decreased from an average of 22.8 at the pretreatment level to 8.7 at 1 week, 8.9 at 4 weeks, 9.3 at 3 months, 7.0 at 6 months, and 7.7 at 12 months. These data indicate that the psilocybin provided persistent relief to many patients [1].

In a 2018 British study, 26 patients, 20 of whom were diagnosed with severe treatment-resistant depression, were administered separate doses of 10- and 25-mg psilocybin one week apart; administration took place in a supportive setting. Nineteen subjects completed the treatment process, including psychological support, and all of the completers reported improved symptoms based on Quick Inventory of Depressive Symptoms (QIDS-SR16) and HAM-D scores. Four patients experienced remission of their depression at week five. Many completers continued to benefit from treatment at three months and six months. Suicidality scores among the patients also significantly fell within the two weeks after treatment [41].

Not all researchers have offered a ringing endorsement of the use of psilocybin. A 2021 study studied 59 patients with moderate-to-severe major depressive disorder. The subjects were administered either two doses of 25-mg psilocybin three weeks apart plus placebo (30 patients) over six weeks, or they were given escitalopram (an SSRI) for six weeks (29 patients). All the patients also received psychological assistance. No significant differences were noted in depression symptoms between the two groups, and the researchers concluded that further studies with larger populations were needed. Even the adverse events in the two groups were somewhat similar; the most common adverse effect in both groups over the course of the study was headache, followed by nausea [42]. Even in this study, psilocybin was about as effective as antidepressant therapy. This is remarkable, in that this new treatment is about as effective as the established criterion standard treatment for major depressive disorder.

Although studies have supported the hypothesis that psilocybin provided under research conditions by physicians has a positive effect on depressive symptoms, until recently, the mechanism by which this improvement has occurred was largely unknown. However, in a study of 16 individuals with treatment-resistant depression, researchers used functional magnetic resonance imaging (fMRI) to assess functional brain changes both at baseline and one day after the study group received 25-mg psilocybin. The researchers found brain network modularity was reduced within just one day after the psilocybin was administered [43]. In a second study by the same researchers, 59 patients with major depressive disorder were randomized to either two doses of 25-mg psilocybin three weeks apart plus six weeks of daily placebo or to six weeks of 10- to 20-mg escitalopram per day plus 1-mg psilocybin (an ineffective dose). In this study, 29 subjects were in the escitalopram arm, although the group ultimately decreased to 21 subjects (28% dropout rate). The 30 patients in the psilocybin group decreased to 22 subjects (27% dropout rate) [43]. The researchers noted that [43]:

> It is plausible that this putative liberating effect of psilocybin on cortical activity occurs via its direct agonist action on cortical 5-HT2A receptors, dysregulating activity in regions rich in their expression. We surmise that chronic escitalopram does not have the effect on brain modularity due to its more generalized action on the serotonin system and predominant action on inhibitory postsynaptic 5-HT1A receptors, which are richly expressed in limbic circuity.

The researchers found that the antidepressant effect of the psilocybin was sustained and rapid and that it also corresponded with decreases in fMRI brain network modularity. This indicates that the antidepressant effect of psilocybin, when it works, is linked with a global increase in brain network integration. In contrast, the response to the escitalopram was mild and caused no changes to the brain network [43].

**KETAMINE**

Ketamine is a derivative of phencyclidine (PCP), which itself was originally developed as an anesthetic. However, the major adverse effects of PCP, such as aggression, psychosis, and dysphoria, made it an undesirable and unacceptable anesthetic choice [44]. In contrast, ketamine was effective as an anesthetic and had few adverse effects. PCP subsequently became a drug of abuse.

While ketamine has been used in operative analgesia for decades, it has also become a drug of abuse and misuse [45]. Most notoriously, ketamine became known as a "date-rape drug," because it was administered in drinks to unknowing victims who were subsequently sexually assaulted by their predators. Because ketamine causes amnesia, victims have little or no memory of what occurred to them, although they

often experienced after-effects, such as pain. As a result of this growing criminal use, Congress passed the Drug-Induced Rape Prevention and Punishment Act of 1996. During this period and the decade following, there was increased awareness of the dangers of ketamine and other drugs that were used in a similar manner, such as flunitrazepam (Rohypnol) and gamma hydroxybutyric acid (GHB) [46]. As a result, ketamine developed a stigma, and this negative view may persist in many minds.

Ketamine is a Schedule III drug that is a combination of s-ketamine (esketamine) and r-ketamine (arketamine). In 2019, the use of esketamine as a nasal spray (brand name Spravato) was approved by the FDA for the treatment of treatment-resistant depression. Since then, it has also been approved to treat suicidal depression. However, it should be noted that this nasal spray formulation is not available at most pharmacies; instead, it is provided solely through a restricted distribution system. The FDA also requires that patients be overseen for a minimum of two hours after treatment, in order to allow sufficient time to identify and address and adverse reactions that develop in patients. (It is not clear if all ketamine clinics adhere to this provision.)

EVIDENCE-BASED PRACTICE RECOMMENDATION

For patients with major depressive disorder who have not responded to several adequate pharmacologic trials, the Department of Veterans Affairs suggests ketamine or esketamine as an option for augmentation.

(https://www.healthquality.va.gov/guidelines/MH/mdd/VADoDMDDCPGFinal508.pdf. Last accessed July 8, 2022.)

**Strength of Recommendation**: Weak for

After treatment with ketamine, patients should not leave the facility until they are cleared to do so by a healthcare provider and they should also be cautioned to avoid driving or using heavy equipment until the following day. In addition, patients are not allowed to take the nasal spray home, because it may only be used in the medical office while under the supervision of qualified staff members [47].

Intravenous ketamine has been used off-label for treatment-resistant depression by some clinicians, and ketamine clinics are established in many parts of the United States, although their fees vary widely. The effects of intravenously administered ketamine may last for hours, days, or even weeks in some patients. Some believe that intravenous ketamine is significantly more effective than its intranasal form because it includes both the s and r forms of the drug.

Some researchers have found that the mental state of the patient (set) prior to receiving treatment with ketamine may affect the outcome of treatment. In a 2019 study, 31 patients with major depressive disorder were treated with ketamine infusions. Researchers used multiple instruments to measure the mental state of subjects prior to and after receiving treatment, including the Montgomery-Asberg Depression Rating Scale (MADRS) and the Beck Hopelessness Scale. In this study, 17 subjects (55%) responded to the ketamine, while 14 (45%) had no response [48]. Non-responders had significantly higher rates on anxiety scales than responders. The researchers stated [48]:

> The present study showed for the first time that non-responders had more anxiety-related experiences induced by the first ketamine infusion than responders confirming our initial hypothesis of significantly different subjective experiences as a function of treatment response. Specifically, we found that it was the extent of ketamine-induced anxiety that was negatively predictive of a treatment response after a series of six infusions on average.

They also noted that providing a calm treatment environment to patients might be sufficient to reduce anxiety levels in patients to improve outcomes. This is the goal of treatment providers as well as researchers who emphasize the importance of set (mindset) and setting, as discussed. In this study, there was no follow-up after the last infusion, which may also have improved efficacy [48].

In another study of 30 individuals with PTSD of a median duration of 15 years, half of subjects were randomized to a ketamine group and half were assigned to a midazolam (a benzodiazepine) group. The subjects received six infusions over the course of two weeks of either ketamine (0.5 mg/kg) or midazolam (0.045 mg/kg). The subjects were evaluated with the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) at baseline and also at the end of treatment [49].

The average CAPS-5 total scores following the infusions were 11.88 points lower among the subjects in the ketamine group compared with the midazolam group. About two-thirds of the ketamine subjects (67%) responded to the treatment, versus only 20% of treatment responders in the midazolam group. The median time to loss of treatment following the two-week ketamine treatment period was 27.5 days. However, in outlier cases, two subjects still had not lost their response; improvements continued at 50 days and 102 days since the last infusion. The ketamine group experienced a major reduction in symptoms of depression as well as in clinical ratings of global psychiatric illness severity. The researchers concluded that the findings from this study support the assertion that "repeated ketamine infusions are safe and generally well tolerated among individuals with chronic PTSD, with only transient emergence of psychoactive and hemodynamic side effects" [49].

In a French study, ketamine was explored as a treatment for individuals with severe suicidal ideation in a double-blind randomized clinical trial. In this six-study report, published in 2022, 156 patients were given either a 40-minute infusion of ketamine or placebo (saline solution). The administration was repeated 24 hours later. The groups were also divided into subjects with bipolar disorder, depressive disorder, and other diagnoses. Of patients in the ketamine group, 93.1% had a past history of the commission of a suicidal act, as did 86.6% of the subjects in the placebo arm [50].

On day 3, nearly two-thirds (63%) of the patients in the ketamine group achieved full remission from suicidal thoughts. In contrast, 31.6% of the patients in the placebo group were in remission. In nearly 44% of the ketamine subjects, remission occurred within two hours after the first infusion, compared with 7.3% of the placebo group. Ketamine was particularly effective in the bipolar group, while its effect was not significant in the group with major depressive or other psychiatric disorders. The researchers speculated that ketamine might provide an analgesic kind of effect to mental pain [50].

**MDMA**

In the past and even to date, MDMA (also referred to as "Ecstasy" or "Molly") has been largely a drug of abuse. According to the National Institute on Drug Abuse, about 2.6 million people in the United States 12 years of age and older reported past-year use of MDMA in 2020 [51]. The drug was originally developed by Merck in 1912, and in the 1970s, it was found to be useful in combination with psychotherapy [52]. However, because of considerable active abuse of the drug in the United States, in 1985, MDMA was categorized as a Schedule I drug under the Controlled Substances Act in an emergency ban, and consequently research on this drug largely halted until the 2010s [53].

Today, researchers have demonstrated the efficacy of combination psychotherapy and MDMA in treating PTSD. The FDA has granted "breakthrough therapy" permission for MDMA therapeutic treatment, largely as a result of the findings of several small studies. Clinicians who use MDMA-assisted psychotherapy to treat individuals with PTSD have access to a manual outlining best practices for this therapeutic use. In the 2017 revision of this manual, the following explanation is given [54]:

> The basic premise of this treatment approach is that the therapeutic effect is not due simply to the physiological effects of the medicine; rather, it is the result of an interaction between the effects of the medicine, the therapeutic setting, and the mindsets of the participant and the therapists. MDMA produces an experience that appears to temporarily reduce fear, increase the range of positive emotions toward self and others, and increase interpersonal trust without clouding the sensorium or inhibiting access to emotions. MDMA may catalyze therapeutic processing by allowing participants to stay emotionally engaged while revisiting traumatic experiences without being overwhelmed by anxiety or other painful emotions. Frequently, participants are able to experience and express fear, anger, and grief as part of the therapeutic process with less likelihood of either feeling overwhelmed by these emotions or of avoiding them by dissociation or emotional numbing. In addition, MDMA can enable a heightened state of empathic rapport that facilitates the therapeutic process and allows for a corrective experience of secure attachment and collaboration with the therapists.

In six double-blind, randomized clinical studies conducted between 2004 and 2017, 72 subjects are administered 75–125 mg of MDMA in two or three sessions, comparing these results with 31 patients who received placebo; all the patients had diagnosed PTSD. The drug was administered following 90-minute sessions of psychotherapy and three to four therapy sessions were also provided during follow-up after MDMA therapy [55].

Members of the treatment group reported significantly reduced scores on the CAPS-5 compared with the control group. In addition, after two sessions, 54.2% of those who received MDMA no longer met the criteria for PTSD—they were in remission. In contrast, only 22.6% of the control group experienced remission. The researchers noted that "MDMA-assisted psychotherapy was efficacious and well tolerated in a large sample of adults with PTSD" [55].

In another randomized, double-blind, placebo-controlled phase 3 clinical trial with 90 individuals with severe PTSD, the subjects received manualized therapy with either MDMA or placebo. Three preparatory sessions occurred before the administration of the drug, and there were nine integrative therapy sessions afterwards. Subjects in the MDMA treatment group experienced a significant decrease in CAPS-5 (-24.4) scores compared with placebo subjects (-13.9). Scores on the Sheehan Disability Scale (SDS) also significantly improved in the MDMA subjects compared with the placebo subjects [56]. The researchers noted [56]:

> Given that PTSD is a strong predictor of disability in both veterans and community populations, it is promising to note that the robust reduction in PTSD and depressive symptoms identified here is complemented by a significant improvement in SDS score (for example, work and/or school, social and family functioning). Approximately 4.7 million U.S. veterans report a service-related disability, costing the U.S. government approximately $73 billion per year. Identification of a PTSD treatment that could improve social and family functioning and ameliorate impairment across a broad range of environmental contexts could provide major medical cost savings, in addition to improving the quality of life for veterans and others affected by this disorder.

Because major problems with sleep quality are common among patients with PTSD, some researchers have studied the effects of MDMA-assisted psychotherapy to determine its effects on sleep disorder. In a series of four studies with 63 subjects at sites in the United States, Canada, and Israel, subjects were randomized to two or three sessions of MDMA-assisted psychotherapy or to a control group. PTSD symptoms were assessed with the CAPS-IV, and the Pittsburgh Sleep Quality Index (PSQI) was used to measure changes in sleep quality. At the conclusion of the study, the CAPS-IV severity scores had decreased by 34 points in the MDMA group, compared with a decrease of 12.4 points for the control group. In addition, sleep quality improved significantly in the experimental group compared with the control group. In the treatment group, 53.2% of subjects reported a PSQI score drop of 3 or more points, compared with 12.5% in the control group [57].

Although there appears to be a benefit for MDMA therapy in the management of PTSD, especially for patients who have failed other therapies, the durability of this affect has been questioned. One study indicated improvement may be persistent for a considerable period of time for some subjects. In a study involving 107 subjects with PTSD, individuals were administered either two or three doses of MDMA (75–125 mg) during blinded or open-label therapy sessions. The subject's PTSD symptoms were evaluated 1 to 2 months after the last MDMA session and again after 12 months. The researchers reported that at the 12-month follow-up time, nearly all (97.6%) of the subjects said they had benefited from the treatment, and 53.2% reported large benefits that had lasted or even increased. A minority of subjects reported unfavorable results; 8.4% reported harms. However, in 86% of these cases (six of seven subjects), the harms were rated as a 3 or less on a 5-point scale. There were no reports of severe harm, and all the subjects who reported harm also reported one or more benefits. The most common harm reported was worsened mood (3.6%) [58]. The researchers noted that, "Overall findings from the present analyses support MDMA-assisted psychotherapy as an efficacious treatment for PTSD with symptom improvements that were sustained at 1 to 3.8 years post-treatment. These findings corroborate and expand preliminary results from the first phase 2 trial of this treatment" [58].

## IBOGAINE

Largely derived from the Western African shrub *Tabernanthe iboga*, ibogaine has been explored as a possible treatment for opioid use disorder, although there are many caveats to be considered, including the fact that ibogaine is a Schedule I drug. Given the current climate surrounding opioid misuse and use disorder in the United States, possible treatment options are a major focus. According to the Centers for Disease Control and Prevention, more than 70% of drug overdoses in the United States in 2019 were related to opioid use [59]. Ibogaine apparently acts to eliminate craving for opioids and rapidly detoxifies individuals with opioid dependence, although much further study with larger populations is needed. Most people who seek treatment with ibogaine have opioid use disorder, but some have been dependent on stimulants such as cocaine.

The anti-addictive capabilities of ibogaine were first noted by Howard Lotsof in 1962 as a result of his own experience with the drug as well as reports from others. Lotsof, a man in recovery from heroin use disorder from New York City who unexpectedly found relief and remission with ibogaine, subsequently actively and tirelessly lobbied researchers to study the drug. He eventually succeeded, and multiple researchers using both animal and human studies have demonstrated ibogaine's apparent ability to induce recovery in some persons struggling with substance use disorders [60; 61].

Metabolism of ibogaine is purportedly mediated by the p450 cytochrome enzyme CY2D6. Because of genetic differences, an estimated 10% of persons of European heritage (predominantly White Americans in the United States) lack the necessary gene to synthesize this enzyme. Among this group, including the many individuals who do not realize they lack this gene, administration of ibogaine can result in plasma levels as much as twice as high as those in persons with the gene. As a precaution, a test dose of the drug may be given to subjects to assess the response. Another option is genotype screening of subjects who seek treatment with ibogaine, to ensure safety and to aid in treatment decisions [62].

Although it provides insufficient data from which to draw major conclusions, a study of the use of ibogaine in two adults with opioid use disorder is interesting. The experiences of one of the patients are described here, although it should be noted that both patients have remained abstinent for several years [62]. The first patient developed an opioid use disorder secondary to pain from chronic pancreatitis. His physician was concerned about potential misuse and weaned the patient off opioids; however, the patient began taking large quantities of oxycodone tablets he purchased illegally. As the substance use disorder progressed, this patient was actively resistant to conventional treatment despite clear physical and psychosocial consequences. Eventually, he agreed to experimental treatment with ibogaine.

The patient was screened with an electrocardiogram prior to treatment and administered a test dose of ibogaine. During the first four days of treatment, he was administered oxycodone (legally obtained via prescription). The opioid doses were steadily titrated down and on day 4, all opioid medications stopped. During this same period, the patient was given increasing doses of ibogaine. On day 4, the patient was given a "flood dose" of both iboga and ibogaine (variations of the same drug). Between treatments, diazepam was given to support sleep and assuage anxiety. Treatment lasted for six days, and the patient remained at the clinic for a total of eight days. At three-year follow-up, the patient had remained abstinent from opioids, as indicated by negative drug screens. Interestingly,

after the flood dose of ibogaine, the client also reported that his chronic pain issues ended, and they have not recurred [62]. The reasons for this finding are unknown.

In a study of 14 individuals with opioid use disorder, subjects were given staggered doses of 200-mg ibogaine capsules at two different clinics. Because ibogaine is a stimulant, most patients were given benzodiazepines or sleep aids so they could attain sufficient hours of sleep. The first dose administered was a test dose given when the patient was in a withdrawal state from opioids; then, a larger dose of up to 600 mg of ibogaine was given one to four hours later. This was followed by smaller dosages of 200 mg given at 20-minute intervals until ended by the provider. The subjects were interviewed pretreatment, immediately post-treatment, and 12 months later. The outcome was that 12 of the 14 subjects (85.7%) had either a marked reduction in opioid use or ended use of the drug altogether [61].

In a larger study of 191 adults wishing to detoxify from opioids or cocaine, a single dose of ibogaine was administered during a medically supervised period of detoxification. According to the researchers, the goals of the study were to safely detoxify the subjects from opioids or cocaine, to provide motivational counseling, and to refer the patients to aftercare and 12-step programs [63]. All subjects received a physical examination, and a medical history was taken. Laboratory tests were administered, as were electrocardiograms. The subjects were drug tested at the beginning of the program, and all tested positive for either opioids or cocaine. A licensed therapist worked with the subjects during and after ibogaine was administered. The average age of subjects was 36 years, and all were habitual users. The subjects were given one dose oral (gel capsule) ibogaine 8–12 mg/kg. In this study, the most common adverse effect was headache, reported by 7% of the subjects; orthostatic hypotension occurred in 5% of the subjects. About 2% of adverse events were considered to be moderately severe.

After the ibogaine was administered, its effects began about 30 to 45 minutes later. According to the researchers [63]:

> Sensory and perceptual changes included reports of visual images, changes in the quality and rate of thinking, and heightened sensitivity to sound. Most subjects reported a dream-like experience lasting between four and eight hours, after which there was an abrupt change in the sensory experience to a more quiet period of deep introspection.

Approximately 92% of subjects reported benefits from the experience. They also reported that both drug craving and depression symptoms improved with doses of 500–1,000 mg. One shortcoming of this study, however, was a lack of follow-up. It would be especially helpful to know if these individuals remained abstinent 6 to 12 months later. Unfortunately, this was not among the goals of the researchers [63].

Ibogaine is difficult to obtain in the United States, and travel to other countries to obtain treatment has been reported, which can be very costly. Assuming that ibogaine were to be equal in efficacy to clonidine or lofexidine for detoxification from opioids or acute discontinuation, it is still unclear what long-term effects or level of continued abstinence can be expected. Naltrexone (Vivitrol) following detoxification might be facilitated. But, data supporting the use of suboxone and methadone in reducing overdoses, deaths, and emergency department visits are clear, including both short- and long-term outcomes. It is important to compare ibogaine to buprenorphine or methadone treatment, just as psilocybin was compared to SSRI therapy [64].

## KRATOM

Kratom is a drug derived from *Mitragyna speciosa,* an evergreen tree native to Southeast Asia, where it has been used for generations, largely by locals who chew on the leaves or brew it into a tea and reportedly use the drug for an energizing purpose (e.g., to facilitate longer work periods), much as Americans use caffeine. Kratom is used by consumers in the United States as a drug of abuse and, less commonly, to manage depression. As of 2022, the drug is not scheduled by the U.S. Drug Enforcement Administration (DEA), although the DEA did consider categorizing kratom constituents mitragynine and 7-hydroxymitragynine under Schedule I in 2016. This effort was met with considerable resistance and was abandoned. As such, the product remains available locally in smoke and "head" shops, although many purchase the drug over the Internet. Kratom is banned in six states, including Arkansas, Indiana, Tennessee, Vermont, Wisconsin, and most recently in Alabama [65].

Experts exploring the potential psychiatric uses of kratom have expressed optimism. According to McCurdy, kratom "seems to have mood lifting and elevating properties in addition to its ability to seem to move people off of hardcore opiates" [66]. Although the drug is traditionally used as a stimulant, it has a sedative or opioid-like effects in very high doses. It has been hypothesized that kratom might have a role in the treatment of opioid use disorder, although much more study is needed.

It is important to note that kratom products available in the United States are very different from those that are used by people in their native environments. For example, the kratom used in Southeast Asia is almost always derived from fresh leaves, while in the United States, the products are freeze-dried leaves, concentrated extracts, or liquid "energy shots." As a result of these differences, concentrations and adulteration are concerns. Some individuals in the West who consume kratom products have displayed blood serum levels of mitragynine (the key alkaloid in kratom) 100 to 1,000 times higher than in those found in consumers in Southeast Asia [67].

Another issue is one of purity. In an analysis of eight samples of the drug, researchers found that all the samples tested positive for varying levels of *Mitragyna,* ranging from 3.9–62.1 mg/g, which is a wide range that could significantly alter efficacy and toxicity [68]. In addition, six of the samples tested positive for fungi and bacteria. Most (seven) of the samples were positive for significant levels of toxic heavy metals, including nickel, lead, and chromium. The presence of lead was particularly troubling, as lead has many potentially toxic effects, particularly in terms of potential problematic neurologic effects in children and young adults as well as a variety of cognitive, developmental, immunologic, renal, and cardiovascular effects [68]. Although this study did not find evidence of *Salmonella* contamination, in 2018, a *Salmonella* outbreak originating from kratom products was reported to affect 199 people spanning 41 states [69]. It is clear that the purity of kratom purchased in the United States is highly questionable, largely because there are no federal constraints on its production by the FDA or other federal agencies. Healthcare professionals who know or suspect that their patients are using kratom may wish to warn them about these findings.

**LSD**

As discussed, LSD is a compound synthesized from ergot. It is usually administered as an oral solution. LSD takes effect within 20 to 40 minutes after ingestion, and its effects may last for up to 12 hours. Flashbacks may also occur with this drug, defined as a feeling of re-experiencing an event or emotion that occurred during the course of the LSD "trip." LSD is about 2,000 times more potent than mescaline [37].

Prior to the Controlled Substances Act passage in 1970, there were numerous research studies on LSD as a treatment for depression, substance use disorder, and other psychiatric diagnoses, although some of these studies were not scientifically rigorous by today's standards. Fewer studies on LSD are published today, but several merit some attention. For example, a 2022 study assessed the impact of LSD on stressed mice [70]. Anxious mice were administered low doses of LSD for seven days, during which their anxiety levels decreased. In addition, researchers found that the mice given LSD showed signs of increased production of new dendritic spines, a sign of brain plasticity. The researchers also found that the LSD increased the production of serotonin in the treated mice, in a somewhat similar manner to SSRI antidepressants [70].

In an earlier study of the effects of LSD on humans with life-threatening diseases, 8 of the 12 subjects were given 200 mcg of LSD and a control group was given 20 mcg, an insufficient dose to generate significant response. After the initial blinded study was unmasked, the control group subjects were also given 200 mcg of LSD. All subjects had a score of higher than 40 on the state or trait scale of the Spielberger State-Trait Anxiety Inventory before the study. In addition, half the subjects had diagnosed generalized anxiety disorder. A therapist was present for two sessions conducted two to three weeks apart. The experimental sessions lasted eight hours, and patients left only to use the restroom [71]. Subjects who received the 200-mcg dose of LSD displayed a decrease in anxiety as measured by multiple instruments, and this decrease persisted at the 12-month follow-up evaluation. Overall, the subjects experienced a 78% drop in anxiety scores and a 67% increase in quality of life scores after one year. They also reported better access to and control of their own emotions [72].

While this research is interesting and points to areas for future research, it remains to be seen if LSD (or a similar compound) will ever be in clinical use for anxiety and depression. In addition to overcoming stigma and issues with adverse effects, significant additional research on efficacy is necessary.

**MESCALINE**

3,4,5-trimethoxyphenethylamine, also known as mescaline, is a psychedelic drug that is mainly found in *Lophophora williamsii*, or the peyote cactus. Its effects upon ingestion are similar to the effects found with LSD or psilocybin, including hallucinations and euphoria [37]. The drug is known to have been used for thousands of years for these and perceived spiritual or medical effects; archaeologists have found evidence of this drug in Texas dating back 5,700 years [73]. Today, it is a Schedule I drug, but it may be used legally in religious ceremonies of the Native American Church. Mescaline has been suggested as a potentially effective treatment for a variety of mental health conditions, including depression, OCD, anxiety, and substance use disorder; however, research has yet to be conducted to support these claims.

The average dose of mescaline ranges from 20–500 mg, and the duration of action is about 10 to 12 hours. Individuals suffering from mescaline toxicity (typically seen with doses of 20 mg/kg or greater) may experience tachycardia, hypertension, seizures, hyperthermia, respiratory depression, and rarely death [73]. Concomitant use of mescaline with stimulant drugs (e.g., nicotine, cocaine, ephedrine, amphetamines) may increase the risk of adverse central nervous system effects.

In a survey of 452 individuals who reported using mescaline, researchers found that the drug was usually used once per year or less frequently, and only 9% of users reported a craving for mescaline. About 50% of users reported established psychiatric diagnoses, including anxiety and depression, and of this group, more than 65% reported that these problems improved after taking mescaline [74]. Clinical studies are necessary to confirm or refute these findings.

In another analysis of these data, nearly 50% of respondents reported their experience with mescaline was either the most meaningful experience of their lives or in the top five most meaningful experiences. Respondents who said they had experienced improvement in psychiatric problems were significantly more likely to also report experiencing mystical/spiritual experiences and psychological insight [75].

## NITROUS OXIDE

Nitrous oxide (chemical formula $N_2O$) is a component familiar to many, as it is commonly used today to facilitate comfort and address anxiety in dental settings. Historically, it has been used in both dental and medical interventions. The origins of nitrous oxide are attributed to Joseph Priestley's discovery in 1772, who referred to it as "dephlogisticated nitrous air" [76]. Anesthetic use of nitrous oxide was discovered by a dentist in 1844, and it was used for this purpose almost solely until the 1980s. The first research into the use of nitrous oxide for neuropsychiatric purposes was published between 1920 and 1950, and in the early 1980s, low-dose titration of nitrous oxide was introduced into medical practice as a possible adjunct to the treatment of psychiatric disorders, including substance use disorders [77]. Before then, it was limited to use as an anesthetic or for analgesia during childbirth. In 1994, the term psychotropic analgesic nitrous oxide was introduced in order to better distinguish anesthetic and nonanesthetic preparations [77].

The anxiolytic action of nitrous oxide is believed to be due to binding at select gamma-aminobutyric acid (GABA) receptors, an action similar to the benzodiazepines [78]. The mild analgesic effect appears to be linked to the endogenous opioid receptor system, as experimental studies have shown that the introduction of opioid receptor antagonists to the brain decreases the analgesic efficacy of nitrous oxide [79].

The route of administration is inhalation via a mask secured to the patient's nose. In the dental setting, the concentration of nitrous oxide is 25% to 50% (usually 30% to 40%) nitrous oxide with oxygen. When utilized in obstetrics, a fixed 50% concentration with oxygen is used [77]. Onset of action can occur in as quickly as 30 seconds, with the peak effects seen in five minutes or less. Unlike the benzodiazepine medications, nitrous oxide is not metabolized in the body. It is eliminated via respiration within minutes after 100% oxygen is inhaled at the conclusion of the intervention [78]. Repeated doses could be problematic, as extended use of nitrous oxide has been linked to vitamin B12 deficiency [76]. As such, serum vitamin B12 level may need to be measured before and after treatment.

Nitrous oxide has been demonstrated to improve the condition of individuals with treatment-resistant depression. A study of 20 subjects with treatment-resistant depression were randomly placed in either a nitrous oxide treatment group (10 subjects) or placebo group (10 subjects). The nitrous oxide group inhaled 50% nitrous oxide/50% oxygen, and the placebo group received 50% nitrogen/50% oxygen. There were two sessions one week apart. At the end of the study, four patients (40%) had a decrease in symptoms of depression and three patients (30%) experienced full remission. In contrast, one patient improved after receiving the placebo (10%) and none of the placebo patients remitted from their depression. The improvements in the nitrous oxide group were rapid, occurring in some cases within as little as two hours of receiving the drug [80]. Adverse events were mild and included nausea and vomiting, headache, and dizziness/lightheadedness. At the time of the second session, some patients in the treatment group experienced a carryover effect from the first week's treatment, as evidenced by sustained improvements in their scores on the Hamilton Depression Rating Scale (HDRS-21).

A separate study was undertaken to determine whether a single solution of 25% nitrous oxide would be as beneficial as a 50% solution. This study included 24 subjects with treatment-resistant depression who were randomly placed in one of three groups. Each group received either 50% nitrous oxide therapy, 25% nitrous oxide therapy, or placebo each month; each patient had the opportunity to receive all three treatments. At the end of the study, 55% of the subjects reported improvement in at least half of their symptoms, while 40% reported full remission [81]. Of interest, the 25% nitrous oxide solution had about the same level of efficacy in reducing depression as the 50% solution; however, there were significantly lower levels of adverse events in the 25% group. For example, 21% of those who had received 50% nitrous oxide concentration reported nausea; this decreased to 5% in the group that received 25% concentration. Further, the incidences of headache and dizziness were 17% and 13%, respectively, in the 50% concentration group, while the rates were 10% and 0% in the 25% group [82]. The study made it clear that with nitrous oxide, a 25% solution administered over one hour could improve treatment-resistant depression. Most of the study patients had failed an average of 4.5 antidepressants before the study, so the results were significant for a group in need of additional treatment options.

## AYAHUASCA/DIMETHYLTRYPTAMINE (DMT)

Ayahuasca is a brew derived from the leaves of *Psychotria viridis*, a shrub found in Amazonian South America, and which contains DMT, a hallucinogenic alkaloid. The brew is also made with the *Banisteriopsis caapi* vine, the bark of which contains ingredients that act as MAO inhibitors.

In a Brazilian study involving 29 subjects with treatment-resistant depression, patients were randomized to receive a dose of either ayahuasca or placebo. Subjects were evaluated on the MADRS at the following points: baseline, day 1, day 2, and day 7 after dosing. They found MADRS scores were significantly lower in the ayahuasca group at all points and all individuals in this group experienced improvements. In contrast, 27% of patients in the placebo group developed worse depression symptoms. However, ayahuasca sickens many people, and most of the subjects who were given this substance felt nauseous and 57% vomited [83].

In another small Brazilian study, six subjects with recurrent major depressive disorder (without psychotic symptoms) were assessed for response to ayahuasca therapy. All individuals were inpatients at a psychiatric unit and were not taking any psychiatric or recreational drugs. The ayahuasca used by the volunteers was plant-based and refrigerated before the study, and each person drank 120–200 mg [84]. All subjects experienced decreases in depression symptoms on days 1 and day 7 of treatment. There were significant decreases in the Brief Psychiatric Rating Scale (BPRS), indicating improvements in both depression and anxiety. There were also statistically significant decreases in scores on the HAM-D and the MADRS. For example, on day 1, there was a 62% decrease on the HAM-D, and a 72% decrease by day 7. On day 14, however, depression symptoms increased. Similar changes were seen with the MADRS scores [84]. About half the volunteers did vomit; however, vomiting did not appear to impact the efficacy of the drug [84]. If ayahuasca is to be considered as a therapeutic option, a way to counteract the emetic effects and make the drug more tolerable to patients is necessary. To date, experts have hypothesized that antiemetic drugs might interfere with the action of ayahuasca.

Another problem with the scientific study of ayahuasca is that the effects of the drug depend on the concoction and there are no standardized dosages. If the drug could be provided in a synthesized form, it would become easier to evaluate and study in patients with depression and other disorders. In Barker's report on DMT, he states [85]:

> While ayahuasca obviously holds promise in many social, cultural, and therapeutic paradigms, including treatment of addiction, anxiety, and depression in psychiatry and many other possible applications, it is, nonetheless, a complex mixture of perhaps thousands of compounds.

DMT has been identified in additional substances. The Sonoran Desert toad (*Bufo alvarius*), native to Texas, California, and Mexico, excretes a venom when threatened that contains a naturally occurring form of DMT. This venom, which can be made into crystals and smoked, is popular for inducing psychedelic trips among recreational users. However, this venom is unsafe, and some have died after smoking it. Further, harvesting this venom has reduced the population of the toad in some areas. Overall, experts recommend that people not attempt to capture the toads or harvest the venom [86].

## DIAGNOSES AND PSYCHEDELIC MEDICINE

This section will outline the possible role of psychedelics in the management of specific psychiatric diagnoses, including diagnoses not previously discussed. It is important to remember that most of these uses are investigational.

### TREATMENT-RESISTANT DEPRESSION AND SUICIDE

Depression and suicidal depression are major problems in the United States. As noted, at least 30% of persons with depression do not respond to psychotherapy and/or medication. Psilocybin has proven effective at providing breakthroughs with treatment-resistant depression as well as in treating suicidal depression [41; 42]. Nasal spray esketamine (Spravato) is FDA-approved as an adjunct treatment in addition to a conventional antidepressant for treatment-resistant depression and/or major depressive disorder with suicidal ideation or behavior [87]. The nasal spray formulation of esketamine is administered in two sprays (28 mg) per device. The recommended dosage for adults with treatment-resistant depression is 56 mg on day 1, then 56–84 mg twice per week for four weeks, reducing to once per week for the next four weeks, and then once weekly or once every two weeks thereafter. This drug is only administered under medical supervision, and patients should remain under observation for at least two hours following administration.

There are concerns regarding misuse, excessive sedation, and diversion, and a Risk Evaluation and Mitigation Strategy (REMS) has been established. The full document is available online at https://www.accessdata.fda.gov/drugsatfda_docs/rems/Spravato_2022_01_03_REMS_Document.pdf.

### PTSD

MDMA and ketamine are well on their way to being proven safe and effective in the treatment of PTSD, and further studies on other psychedelics are likely to provide even more breakthrough information. According to the National Center for PTSD, an estimated 12 million adults in the United States have PTSD in a given year; 8% of women and 4% of men develop PTSD in their lifetime [88]. However, PTSD is very difficult to treat with medications and psychotherapy.

The usual dosage of ketamine for the treatment of persistent PTSD is 0.5 mg/kg given via a 40-minute IV infusion. The regimen typically consists of multiple sessions per week for two to four weeks [89].

In the research setting, MDMA for PTSD is typically given during or immediately preceding a psychotherapy session. The usual dose is 75–125 mg in a single dose [90]. As a Schedule I drug, MDMA is only used in clinical trials and research settings.

## SUBSTANCE USE DISORDERS

To date, psychedelic drugs such as ibogaine have not been proven effective in treating opioid use disorder and may not compare well to existing and approved treatments. However, limited studies have shown decreased substance use after administration of psilocybin and ketamine. A 2014 open-label pilot study married a 15-week smoking cessation program with several doses of psilocybin. This study included 15 smokers who were considered psychiatrically healthy adults who had smoked an average of 19 cigarettes per day for an average of 31 years [91]. Psilocybin was administered during the 5th, 7th, and 13th week of the study. During the first four weekly meetings, cognitive-behavioral therapy was provided as was preparation for receiving psilocybin. A target quit date was set to occur with the first dosage of psilocybin during week five, when the subjects were given 20 mg/70 kg of psilocybin. Weekly meetings continued, and then on the seventh week, a higher dose of 30 mg/70 kg was given. During the 13th week, the higher dose of psilocybin was made optional for the subjects. Before the psilocybin was administered, subjects noted their motivational statement for smoking cessation. The subjects also participated in a guided imagery exercise at the end of the first psilocybin session [91]. At six-month follow-up, 80% of the former smokers (12 of 15) were abstinent from tobacco, as verified by breath and urine tests. This was a much higher abstinence rate than seen with traditional smoking cessation programs [91].

The researchers returned to their subjects later, reporting on smoking abstinence at 12 months and over the long term, with an average of 30 months after the study. They found that at the 12-month point, 67% were abstinent from smoking. At the long-term point, 60% were still smoking-abstinent, an excellent success rate [92].

In an older study of single versus repeated sessions of ketamine-assisted psychotherapy in 59 subjects who had detoxified from heroin, subjects were divided into two groups. The subjects in the first group received two addiction counseling sessions with ketamine, followed by two ketamine-assisted psychotherapy sessions, with sessions held at monthly intervals. The subjects in the second group received two addiction counseling sessions without ketamine and one ketamine therapy session. At the one-year follow-up point, 50% of subjects in the first group were still abstinent from heroin, versus 22.2% of subjects in the second group. The researchers concluded that three sessions in the ketamine-assisted psychotherapy program was more effective in promoting abstinence from heroin than one session followed by counseling [93]. There are also emerging data showing positive effects in alcohol use disorders and other substance use disorders.

It is important to keep in mind comparable efficacy. For opioid use disorder, it is vital to know both short- and long-term safety and efficacy comparisons to the standard of care (medication-assisted treatment plus therapy). Also consider that psychedelics will not be proved safe and effective by a professional consensus but rather by the FDA. It may be that psychoactive substances are legalized much in the same fashion cannabis has, but whether they are approved for clinical use will depend on the outcomes of Phase 2 and 3 FDA-qualifying clinical trials and safety and comparable efficacy trials. As of 2022, these trials are ongoing.

## ANXIETY AND DEPRESSION RELATED TO LIFE-THREATENING DIAGNOSES

As discussed, research has demonstrated that psilocybin can be effective in improving mood and quality of life of patients with terminal cancer diagnoses. This aspect of cancer care has been largely overlooked and undertreated. Agrawal notes that, "Oncologists are well-equipped to fight the physical threats of cancer with powerful, yet sometimes imperfect tools including chemotherapy, radiation, and surgery, but they often feel helpless when it comes to treating the intense psychological agony many patients experience" [94]. A seminal study published in 2016 explored the use of a modest dose of psilocybin given to patients with terminal cancer under the supervision of trained therapists. The findings demonstrated that more than 80% of 51 patients who had received life-threatening cancer diagnoses and who subsequently developed depression or anxiety experienced significant and sustained improvements in mood and quality of life six months after taking psilocybin. In addition to feeling calmer and happier, the participants reported forging a closer connection with their friends and family [95]. This study demonstrated the careful and controlled use of psilocybin might be a safe and effective treatment for existential anxiety and despair that often accompany advanced-stage cancers. In addition, in limited studies, LSD has been found to significantly decrease anxiety levels in patients with life-threatening diseases.

Oncology and palliative care specialties have been associated with relatively high burnout rates, at least in part from seeing the psychological distress of patients with potentially terminal diagnoses. In this setting, any therapy that can improve patients' experiences and mood would be beneficial, and initial results of research incorporating psilocybin, LSD, and other psychedelics has been positive [94]. Agrawal further states [94]:

> I have never witnessed the sort of dramatic response to any medical intervention as I have with some patients through psychedelic-assisted therapy. It is not a magic bullet or cure for a cancer patient's suffering—and it won't change their prognosis or life expectancy. But it could be a spark that begins their healing journey, helping them come to terms with their most difficult fears.

The use of psychedelic medications in end-of-life care is logical and should be tested compared to the standard treatment (counseling) in randomized, blind clinical trials and other investigations to facilitate FDA approval.

## OBSESSIVE-COMPULSIVE DISORDER

OCD can be an extremely debilitating disorder that is often difficult to treat. In a 2006 study of nine subjects with treatment-resistant OCD who were treated with psilocybin, the subjects experienced a significant decrease (range 23% to 100%) in OCD symptoms. One of the subjects experienced an issue with temporary hypertension. These are positive findings; however, it is obviously a very small study and additional research would be needed to replicate findings in a larger and more diverse group [96].

Other researchers have discussed the potential for the use of ketamine and esketamine in treating OCD [97]. In a 2013 randomized, double-blind, placebo-controlled, crossover study of drug-free adults with OCD, subjects were given two 40-minute intravenous infusions, one of saline and one of ketamine (0.5 mg/kg), spaced at least one week apart [98]. Individuals who received ketamine reported significant improvement in obsessions (measured by OCD visual analog scale) during the infusion compared with those given placebo. One-week post-infusion, 50% of those who had received ketamine met the criteria for treatment response (defined as a 35% or greater reduction in Yale-Brown Obsessive-Compulsive Scale scores); no subjects receiving placebo displayed treatment response after one week. The authors of this study concluded that "rapid anti-OCD effects from a single intravenous dose of ketamine can persist for at least one week in some patients with constant intrusive thoughts" [98]. However, other studies have found no effect on OCD symptoms [99]. Solid evidence is lacking and requires greater and more rigorous research.

## SOCIAL ANXIETY IN PATIENTS WITH AUTISM

In a study of 12 adults with autism and issues with severe social anxiety, subjects were randomized to receive either MDMA (75 mg or 125 mg) or placebo during the course of two 8-hour psychotherapy sessions. The MDMA was administered after a guided progressive muscle relaxation exercise. The experimental sessions were held one month apart and separated by three nondrug sessions of psychotherapy. The patients were provided with as few sensory interruptions as possible, such as soft lights, noise abatement, and fidget objects to help them with self-regulation through repeated actions (i.e., "stimming") [100]. On the Leibowitz Social Anxiety Scale, the MDMA group experienced a significantly greater improvement in social anxiety scores compared with the placebo group. Improvements persisted at six-month follow-up. The researchers said of the follow-up, "social anxiety remained the same or continued to improve slightly for most participants in the MDMA group after completing the active treatment phase" [100].

Social anxiety disorder is relatively common among the general population; about 12% suffer from this disorder at some point in their lives [101]. If it is determined to be an effective treatment, MDMA-assisted psychotherapy could be an option for these patients who have not responded to traditional psychotherapy or pharmacotherapy.

## ANOREXIA NERVOSA

Anorexia nervosa is a severe eating disorder characterized by restriction of energy intake relative to an individual's requirements, typically resulting in low body weight and malnutrition. It is notoriously difficult to treat and has a high mortality rate. Experts have continued to search for more effective treatment options for this population.

In one study, the authors treated 15 patients (23 to 42 years of age) with treatment-resistant anorexia nervosa with infusions of 20 mg/hour of ketamine over 10 hours. The subjects were also given 20 mg twice per day of nalmefene. The subjects showed a marked decreased in scores on compulsion. Before the ketamine was administered, the average scores were 44.0; after treatment, mean compulsion scores dropped to 27.0. Nine of the subjects (60%) showed remission after two to nine ketamine infusions over the course of five days to three weeks [102]. The authors reported the following details on three specific patients [102]:

> Patient 4 increased her weight after three treatments but agreed to more in the hope that her compulsion score would come down further. After a year in follow-up with a normal weight, she then started work and remained in a stable state while followed-up for nine months.
>
> Patient 5 was a married woman and reached a normal weight after five treatments. As an outpatient, her periods returned and she had a successful pregnancy. Patient 6 had a long history of alternating anorexia and bulimia. After four treatments and despite only a small fall in compulsion score, she became able to control her eating and her weight. She held a responsible job with no relapse during two years of follow-up.

In a 2020 study with only one subject, the researchers treated a patient, 29 years of age, who had developed anorexia nervosa at 14.5 years of age and had been unable to attain remission. The researchers prescribed a ketogenic diet along with intravenous ketamine infusions. (A ketogenic diet was chosen because it had proven in the past to prevent starvation, a real risk with anorexia.) The patient sustained complete recovery and continued her ketogenic diet while maintaining a normal weight [103]. After three months, the woman remained on the ketogenic diet and reported feeling significantly better but still suffered from anorexic compulsions. At that time, she was sent for ketamine infusions. The patient reported that within

one hour of her first infusion the "anorexic voice" inside her was decreasing and she felt more like herself. The patient had three more infusions over the next 14 days. After the fourth infusion, the patient stated [103]:

> I know this sounds ridiculous, but I am no longer anorexic. I had so many rules I didn't even know them. But they are gone. I can exercise because it feels good. It isn't that I have to. I can stop when I want to.

Because this study had two potentially essential factors (ketamine and the ketogenic diet), it is unclear if either or both are responsible for the single patient's improvements. As is the case for many of these novel treatments, additional research is warranted.

### CLUSTER HEADACHES

Cluster headaches, which affect less than 1% of adults, are considered to be the most painful of all headaches and can last for a week or longer, potentially becoming a chronic health issue [104]. Traditional treatment approaches include triptan medications and oxygen therapy. Understandably, most sufferers seek quick relief and would prefer to never experience another attack.

In one report, the authors interviewed 53 people with cluster headaches who had self-medicated with psilocybin or LSD. (This is not recommended or considered safe.) Of 26 patients who used psilocybin, 22 said the drug successfully aborted their headache attacks. Of five people who said they used LSD to treat their headaches, four reported experiencing remission [105]. Based on these findings, the authors recommend further study of psychedelics as a possible treatment for cluster headaches. It is important to remember that self-reports are no basis for concluding that psilocybin or LSD is effective at improving a cluster headache condition. There is a current clinical trial underway examining the role of LSD as a possible treatment for cluster headaches [106].

In another study of 77 patients with treatment-resistant migraines or new daily headaches, all of whom had failed aggressive outpatient and inpatient treatment, patients were infused with ketamine. According to the researchers, the mean headache pain rating at the start of the study was 7.1; this fell to 3.8 upon discharge. Most of the patients responded well to the ketamine. Researchers concluded [107]:

> Pending higher level evidence and given that ketamine is generally well-tolerated, ketamine may be considered a reasonable acute treatment for well-selected headache patients for whom standard therapies are either ineffective or medically contraindicated.

### OTHER DISORDERS

Some psychiatric disorders, particularly those with psychotic features such as schizophrenia, schizophreniform disorder, brief psychotic disorder, schizoaffective disorder, and delusional disorder, should certainly not be treated with psychedelic drugs. It is unclear if other psychiatric conditions would be amenable to psychedelic treatment. This can only be determined by clinical trials that administer these drugs under scientific rigor and with a sufficiently high number of patients. Many of the studies published to date have included very small numbers of patients, though this is largely because of necessity. It may have been that few individuals with the disorder could be recruited into a trial consisting of experimental treatment with a psychedelic drug. As the knowledge base grows based on clinical trials, it is hoped that it will become increasingly more feasible to test psychedelics on patients with a multitude of psychiatric disorders, particularly for those individuals whose conditions have been challenging to treat.

## INTERVENTIONAL PSYCHIATRY: BRAIN STIMULATION THERAPIES

Electroconvulsive therapy has been in use for nearly a century and continues to be used in psychiatric treatment today. Newer forms of brain stimulation are increasing popular options for patients—or likely will be soon at major medical centers, including rTMS, VNS, and DBS. New brain mapping techniques may help eliminate the need for more invasive procedures. Interventional psychiatry represents an opportunity to help patients who otherwise have found no relief from pharmacotherapy and standard treatments [108].

For health professionals interested in the latest techniques on neuromodulation to aid patients with refractory psychiatric disorders, interventional psychiatry may be the answer. In order for physicians to effectively enter this field, experts recommend an additional year of training with an emphasis on interventional psychiatry.

### ELECTROCONVULSIVE THERAPY

ECT has been used to treat depression, bipolar disorder, schizophrenia, and other psychiatric diagnoses for many years, starting in the first half of the 20th century. The goal of ECT is to induce a seizure through applied electric shocks. The procedure was initially introduced in the late 1930s in Italy, and in the 1940s through the 1960s, ECT became popular in the United States as a mainstream treatment [109]. However, early treatments did not provide anesthesia and sometimes led to physical and psychological trauma [110]. Physicians later learned that significantly milder shocks could achieve the same goals.

Today, the procedure is used rarely for treatment-resistant depression and major depression with suicidal ideation or behaviors, as well as for schizophrenia and schizoaffective disorder. A team of professionals are involved, including a psychiatrist, a neurologist, an anesthesiologist, and a nurse [110]. Some believe that ECT should be used before psychedelics or newer brain intervention therapies are attempted, although agreement on this subject is not universal. It should also be noted that there is some residual fear/concern of ECT itself that persists among many patients (and some healthcare professionals), largely because ECT was historically traumatic. However, ECT has proven highly effective at treating both major depressive disorder and suicidal depression. About 100,000 patients receive ECT each year, and most of them are residents in psychiatric hospitals or psychiatric units of hospitals [111].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The National Institute for Health and Care Excellence recommends clinicians consider electroconvulsive therapy (ECT) for the treatment of severe depression if the person chooses ECT in preference to other treatments based on their past experience of ECT and what has previously worked for them OR a rapid response is needed (e.g., if the depression is life-threatening) OR other treatments have been unsuccessful.

(https://www.nice.org.uk/guidance/ng222. Last accessed July 8, 2022.)

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

The modern use of ECT consists of [112]:

> induction of brief general anesthesia (typically lasting less than 10 minutes), pharmacologic muscle relaxation, and continuous monitoring of oxygen saturation, blood pressure, and heart rate, and rhythm. An electrical charge is delivered to the brain through scalp electrodes, which results in a generalized seizure typically lasting for 20 to 60 seconds. Most patients receive between 6 and 12 treatments spaced over a period of 2 to 4 weeks as an initial course of treatment.

Patients who receive ECT may have mild-to-moderate cognitive side effects that generally resolve within days or weeks after the course of treatment has ended [112]. Improvement in depressive symptoms is apparent as soon as the third treatment, and remission rates may be as high as 60% among patients with treatment-resistant depression [113].

In a study of 31 patients with major depressive disorder who received ECT treatment, neurocognitive function was assessed with multiple tests, such as the MATRICS Consensus Cognitive Battery, the Everyday Memory Questionnaire, and the MADRS. These instruments were used before ECT, six weeks after ECT, and six months after the procedure. There was a significant decrease in depression scores six weeks and six months after ECT. Patients also exhibited significantly improved neurocognitive abilities six weeks subsequent to the ECT; these improvements were maintained at six months. The researchers concluded that improvements in depression and stability of subjectively reported memory function indicate that the antidepressant effects of ECT do not occur at the expense of cognitive function [114].

A Swedish analysis of 254,906 sessions of ECT conducted with 16,681 individuals between 2012 and 2019 found that fewer than 1% of individuals suffered broken teeth incurred as a result of their treatment. More specifically, the rate was 0.3% per individual, and there were no differences found between patients by age, gender, or diagnosis, although the dental fracture group had a greater number of treatments. Despite the low rate, bite guards and muscle relaxants are recommended to be used as a safety precaution during treatment with ECT [115].

In a 2021 survey of 192 ECT physician practitioners in the United States, 30% of the survey respondents had graduated from one of 12 residency programs in the United States. Several barriers to ECT programs were identified, stigma against ECT on the part of patients and problems with patient transportation, because patients cannot drive themselves home after treatment [116]. With regard to starting a new ECT program, barriers included lack of well-trained ECT practitioners, lack of institutional support or interest in leading the initiative, and insufficient physical space at the facility. The highest concentration of ECT providers were based in New England, and the lowest concentration was in the southern central region of the United States. Overall, the researchers were able to identify a variety of institution-related barriers (e.g., finances, bureaucracy, stigma, lack of understanding) that prevent enthusiastic adoption of this intervention. As a result, although ECT potentially could provide relief to many patients with treatment-resistant depression and other disorders, it may not be an option for many patients who live remotely from centers that offer this service.

In a 2018 study, a MarketScan database of more than 47 million patients was analyzed to determine the incidence of ECT. Of about 1 million patients with a mood disorder, 2,471 (0.25%) had received ECT. Individuals who had received ECT were five times more likely to have additional comorbid psychiatric disorders and twice as likely to have comorbid substance use disorder [117]. Whether ECT should be used more frequently is beyond the scope of this course, but it is important to understand that is can be an effective treatment even though it remains rarely used.

## TRANSCRANIAL MAGNETIC STIMULATION (TMS)

TMS, a noninvasive form of neural modulation, was initially developed in the 1980s. Later, it was discovered that repeated sessions of TMS (rTMS) were more effective than a single treatment. In 2008, the FDA approved rTMS to treat major depressive disorder; in 2018, it was approved to treat OCD [118]. Trials are also investigating the efficacy of rTMS in the treatment of substance use disorders with alcohol, opioids, cannabis, tobacco, methamphetamine, and cocaine [119]. The procedure is also used to treat patients with neurologic disorders, including Parkinson disease, multiple sclerosis, and stroke [120].

An increasingly popular procedure in the United States and other Western countries, rTMS is available at major medical centers throughout the country. This procedure uses large magnets to stimulate the neurons in the prefrontal cortex of the brain. An electromagnetic coil is placed on the patient's forehead at the site of the left prefrontal cortex, an area of the brain that often displays reduced activity in persons with severe and refractory depression. Nonpainful electromagnetic pulses pass through the skin and to the brain. There is no anesthesia needed or given with this procedure, and the only potential adverse effects are headache and minor discomfort in the scalp.

In a U.S. study involving 247 adults with severe treatment-resistant depression, the efficacy of rTMS in improving psychiatric symptoms was evaluated. The average age of the subjects was 43 years, and the average Patient Health Questionnaire-9 score was 21.7. The subjects received single 37-minute sessions over six weeks, up to a maximum of 30 total sessions [121]. Following rTMS therapy, there was a remission rate of 72% after three weeks, with no differences in response by sex of the subject, but age was a factor, with older individuals taking a longer time to achieve remission of their depression. In addition, remission correlated with past suicide attempts, previous psychiatric hospitalizations, and substance use disorder, illustrating that the procedure was highly effective for individuals with severe and/or comorbid disease. In this study, there was a higher efficacy with the MagVenture device compared with the NeuroStar device.

A Dutch study randomized 14 patients with alcohol use disorder to 10 days of rTMS therapy and 16 patients to sham rTMS. The patients were subsequently evaluated for alcohol craving and alcohol use. For a period of time, subjects in the rTMS treatment group reported lower levels of alcohol craving and use than those in the control group. Differences in alcohol craving in the study group were most prevalent 3 months after treatment; at the 12-month point, there were no differences between the two groups, indicating the beneficial effects of rTMS may fade over time [122].

Because rTMS is a safe and effective FDA-approved treatment for depression, some experts have recommended turning the treatment algorithm for depression upside down, putting TMS in a first-choice position. Rather than requiring patients to undergo months of potentially ineffective antidepressant trials, starting with TMS (with an artificial intelligence component to ensure the right dose and optimal targeting) may be a better option [123]. Additional studies are underway to examine TMS and expand evidence-based access to this treatment [123].

Another form of TMS, Stanford accelerated intelligent neuromodulation therapy (also known as Stanford neuromodulation therapy or SAINT), has been associated with an extremely high success rate in patients with treatment-resistant depression. In a 2022 study, nearly 80% of 29 subjects who had been depressed for a mean period of nine years experienced remission in just four weeks. This is a much quicker response time than traditional antidepressant therapy. The difference between SAINT and other TMS procedures lay with a greater number of treatments for a shorter time frame, such as 10-minute sessions 10 times per day. These treatments are also more targeted to the patient's brain circuitry [124].

## VAGUS NERVE STIMULATION

VNS is an invasive form of neuromodulation consisting of implantation of a device that sends electrical pulses to the vagus nerve of the brain. The vagus nerve (also referred to as cranial nerve X) is very long and extends from the brain into the neck, chest, and abdomen. This nerve has many effects and impacts such diverse functions as mood, digestion, blood pressure, heart rate, immune function, saliva production, and taste [125].

The first VNS event occurred in the 1880s in New York, when James Corning applied an electrical current to a carotid compression fork, believing this approach would prevent or end seizures [126]. The procedure has evolved drastically to become the sophisticated procedure used today.

In 2005, the FDA approved VNS for the management of treatment-resistant depression [127]. Since then, a transcutaneous form of VNS has been developed, eliminating the need for surgery. However, this approach was not approved by the FDA as of 2022.

Some researchers have noted that cognitive dysfunction may accompany depression and be a factor in the associated reduced work productivity. A Canadian study analyzed the cognitive performance of individuals with treatment-resistant depression subsequent to their treatment with VNS. In 14 subjects, both the learning capabilities and memory of the subjects improved significantly after one month of receiving VNS. These cognitive improvements persisted for years subsequent to treatment with

VNS. After VNS, 29% of the subjects experienced remission from treatment-resistant depression after 1 month, 50% after 3 months, 57% at 12 months, and 64% at 24 months. As such, at the end of the study, nearly two-thirds of patients had recovered with VNS therapy [128]. The researchers stated [128]:

> Improvements were observed in measures of psychomotor speed, verbal fluency, attention, and executive functioning, as well as verbal and visual memory. We observed clear differences in improvement rate between cognitive measure. Memory measures, such as recall of a complex figure, as well as learning and recall of a word list, show more than 25% improvement after two months of treatment.

## DEEP BRAIN STIMULATION THERAPIES

An invasive form of therapy that is used infrequently, DBS has proven effective at treating severe depression and OCD. DBS is also approved to treat some patients with severe, refractory neurologic disorders, such as epilepsy and Parkinson disease. DBS is also under investigation for the treatment of schizophrenia, Alzheimer disease, substance use disorder, and other challenging psychiatric disorders [129].

The first documented use of DBS occurred in 1948, when neurosurgeon J. Lawrence Pool implanted an electrode into the brain of a women with anorexia and depression. Results were initially positive, until the wire broke several weeks later [130]. Today, DBS involves the permanent implantation of electrodes that send regular and continuous electrical impulses to stimulate a specific part of the brain. Some describe DBS as a sort of brain pacemaker to correct imbalances, comparable to a heart pacemaker that corrects cardiac abnormalities. It should be noted that DBS is an invasive and expensive procedure that is only available to very few individuals, and it is not approved for the treatment of depression by the FDA as of 2022.

The electrodes used in DBS are made of platinum-iridium wires and nickel alloy connectors, which are enclosed in a polyurethane sheath [129]. Some patients may worry about the potential for hacking into a DBS system in today's connected world and the possibility of control over individuals, referred to as "brainjacking." This does not appear to be a problem at this time of very limited use of DBS, but it is a subject worthy of consideration in the future.

In a nationwide database of 116,890 hospitalized patients in the United States with major depressive disorder, patients receiving DBS represented 0.03% [131]. The average age of participants was 49.1 years; all were White, and 88% were female. Patients stayed in the hospital for 1 to 1.6 days. The highest rate of DBS use occurred in the southern United States, followed by the northeast and west. Patients receiving DBS either had private insurance or they were self-pay patients [131].

In a study of five patients with severe OCD who received DBS over the period 2015–2019, not only did the patients experience improvement in their OCD symptoms after DBS, but they also experienced a 53% improvement in their levels of depression (on the MADRS scale) and a 34.9% improvement on the Hamilton Anxiety Rating scales. In addition, patients also improved on the Quality of Life Enjoyment and Satisfaction Questionnaire [132]. The researchers reported anecdotal evidence of improvement as well, such as this report from one of the five patients [132]:

> Despite persistent low body mass index [BMI] of 14, she has remained out of the hospital for 29 months, the longest time period since onset of OCD and anorexia. She is working part-time as a research assistant, is active in her church, and though she wishes for further reduction in symptoms, she notes her quality of life and mood is better than prior to DBS. In addition, she no longer engages in self-injurious behaviors and no longer experiences suicidal ideation.

In another study, DBS was used to treat seven patients with treatment-resistant depression [133]. Researchers specifically targeted the bilateral habenula, which is the seat of the anti-reward system [133]. After one month, depression and anxiety symptoms had decreased by 49%, and the patients reported a dramatic improvement in their quality of life.

In a one-person study of an individual treated with DBS for treatment-resistant depression, the patient experienced continuous improvement until depressive symptoms remitted by the 22nd week. At 37 weeks, the subject was randomized to continuous treatment or discontinuation. When treatment was stopped, the patient reported increasingly worse depression and anxiety until he met rescue criteria, resulting in the resumption of treatment. The depression symptoms rapidly abated when treatment restarted [134].

## CAUTIONS

Although the news about both psychedelics and brain stimulation techniques is generally positive, caution is important, particularly in the case of psychedelic drugs. Patients should be actively discouraged from trying psychedelic drugs on their own, because these drugs can trigger an underlying psychosis in individuals who would otherwise likely have remained healthy, particularly because dosage and purity of the illicit drug is unpredictable. In addition, FDA-approval processes, regulated pharmaceutical drugs rather than street drugs, and comparable efficacy can help identify the safest and most effective medication or interventional treatment for a particular patient at a particular time. In essence, buying MDMA and taking it is not the same as being administered MDMA in a PTSD clinical trial at a research institution. Today, adulteration of street drugs is of great concern, particularly with potentially lethal doses of fentanyl [135].

Patients have no idea what dosage is in a street drug and could take a suboptimal dose (to no effect) or take an excessively high dose of the drug, which could cause inadvertent harm. Importantly, patients under the influence of such drugs require supervision, lest they take actions that might be potentially dangerous to themselves or others.

For patients considered for psychedelic or interventional psychiatric options who are not proficient in English, it is important that information regarding the risks associated with the use of psychedelics and/or interventional procedures 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.

## CONCLUSION

It is apparent that psychedelic medicine is now in a renaissance period, and this time could not have come too soon. Many people in the United States and around the world suffer from severe psychiatric disorders, including depression, PTSD, substance use disorders, anxiety disorders, OCD, anorexia nervosa, and multiple other psychiatric disorders that are not readily responsive to treatment with pharmacotherapy and/or psychotherapy [136]. In the aftermath of the COVID-19 pandemic, depressive disorders are more prevalent, and people are urgently and actively seeking effective treatments. Exploration of novel interventional and psychedelic therapies may be a path to recovery for patients with mental health disorders who have not improved on traditional approaches [137].

## FACULTY BIOGRAPHY

**Mark S. Gold, MD, DFASAM, DLFAPA**, is a teacher of the year, translational researcher, author, mentor, and inventor best known for his work on the brain systems underlying the effects of opiate drugs, cocaine, and food. Dr. Gold was a Professor, Eminent Scholar, Distinguished Professor, Distinguished Alumni Professor, Chairman, and Emeritus Eminent Scholar during his 25 years at the University of Florida. He was a Founding Director of the McKnight Brain Institute and a pioneering neuroscience-addiction researcher funded by the NIH-NIDA-Pharma, whose work helped to de-stigmatize addictions and mainstream addiction education and treatment. He also developed and taught courses and training programs at the University of Florida for undergraduates and medical students. He continues on the Faculty of the University of Florida, Tulane, and Washington University in St Louis.

He is an author and inventor who has published more than 1,000 peer-reviewed scientific articles, 20 text books, popular-general audience books, and physician practice guidelines. Dr. Gold was co-inventor of the use of clonidine in opioid withdrawal and the dopamine hypothesis for cocaine addiction and anhedonia. Both revolutionized how neuroscientists and physicians thought about drugs of abuse, addiction, and the brain. He pioneered the use of clonidine and lofexidine, which became the first non-opioid medication-assisted therapies. His first academic appointment was at Yale University School of Medicine in 1978. Working with Dr. Herb Kleber, he advanced his noradrenergic hyperactivity theory of opioid withdrawal and the use of clonidine and lofexidine to ameliorate these signs and symptoms. During this time, Dr. Gold and Dr. Kleber also worked on rapid detoxification with naloxone and induction on to naltrexone.

Dr. Gold has been awarded many state and national awards for research and service over his long career. He has been awarded major national awards for his neuroscience research including the annual Foundations Fund Prize for the most important research in Psychiatry, the DEA 30 Years of Service Pin (2014), the American Foundation for Addiction Research's Lifetime Achievement Award (2014), the McGovern Award for Lifetime Achievement (2015) for the most important contributions to the understanding and treatment of addiction, the National Leadership Award (NAATP) from addiction treatment providers for helping understand that addiction is a disease of the brain, the DARE Lifetime Achievement Award for volunteer and prevention efforts, the Silver Anvil from the PR Society of America for anti-drug prevention ads, the PRIDE and DARE awards for his career in research and prevention (2015), and the PATH Foundation's Lifetime Achievement Award (2016) as one of the "fathers" of addiction medicine and MAT presented to him by President Obama's White House Drug Czar Michael Botticelli. He was awarded Distinguished Alumni Awards at Yale University, the University of Florida, and Washington University and the Wall of Fame at the University of Florida College of Medicine. Gold was appointed by the University President to two terms as the University's overall Distinguished Professor, allowing him to mentor students and faculty from every college and institute. The University of Florida College of Medicine's White Coat Ceremony for new medical students is named in his honor.

Since his retirement as a full-time academic in 2014, Dr. Gold has continued his teaching, mentoring, research, and writing as an Adjunct Professor in the Department of Psychiatry at Washington University and an active member of the Clinical Council at the Washington University School of Medicine's Public Health Institute. He regularly lectures at medical schools and grand rounds around the country and at international and national scientific meetings on his career and on bench-to-bedside science in eating disorders, psychiatry, obesity, and addictions. He continues on the Faculty at the University of Florida College of Medicine, Department of Psychiatry as an Emeritus Distinguished Professor. He has traveled extensively to help many states develop prevention, education, and treatment approaches to the opioid crisis.

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

## COURSE TEST - #96790 PSYCHEDELIC MEDICINE AND INTERVENTIONAL PSYCHIATRY

*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 June 30, 2025.***

**1. Which of the following is a category of psychedelic drugs?**
- A) *Classic*
- B) *Natural*
- C) *Prescription*
- D) *Hallucinogenic*

**2. Psilocybin has been legalized for consumer use in**
- A) *Oregon.*
- B) *California.*
- C) *New York.*
- D) *New Mexico.*

**3. A hallucinogen is**
- A) *an illicit drug of abuse in all cases.*
- B) *any substance that allows for intensified experiences.*
- C) *a drug that is used to facilitate guided imagery exercises.*
- D) *any drug that may cause the user to experience visual, auditory, or other types of hallucinations.*

**4. In the context of psychedelic medicine, set refers to**
- A) *the patient's mindset.*
- B) *the process of providing effective therapy.*
- C) *the environment in which therapy is provided.*
- D) *the manual of best practices established for therapy.*

**5. Ketamine is considered a**
- A) *Schedule I drug.*
- B) *Schedule II drug.*
- C) *Schedule III drug.*
- D) *non-scheduled drug.*

**6. In the 1940s, LSD was marketed under the brand name Delysid for the treatment of**
- A) *neurosis.*
- B) *alcoholism.*
- C) *schizophrenia.*
- D) *All of the above*

**7. Patients who receive psychedelic therapy experience better outcomes if the therapy is administered in settings in which**
- A) *they feel safe.*
- B) *they are completely alone.*
- C) *everything is new or unfamiliar.*
- D) *hallucinogenic effects are promoted by loud music and flashing colors.*

**8. Which of the following is an aspect of psychedelic medicine setting that can enhance set?**
- A) *Music*
- B) *Lighting*
- C) *Presence of a supportive healthcare professional*
- D) *All of the above*

**9. Which of the following statements regarding psilocybin is FALSE?**
- A) *The duration of action is four to six hours.*
- B) *It is active orally at doses of around 10 mg.*
- C) *Time to onset of effect is usually within 20 to 30 minutes of ingestion.*
- D) *It is about 20 times stronger than LSD but much less potent than mescaline.*

**10. Nasal spray esketamine is approved by the FDA for the treatment of**
- A) *schizophrenia.*
- B) *cluster headaches.*
- C) *opioid use disorder.*
- D) *treatment-resistant and/or suicidal depression.*

*Test questions continue on next page* ➜

**11. Researchers have demonstrated the efficacy of combination psychotherapy and MDMA in the treatment of**
- A) *PTSD.*
- B) *depression.*
- C) *end-of-life anxiety.*
- D) *obsessive-compulsive disorder.*

**12. Which of the following statements regarding ibogaine is TRUE?**
- A) *It is a derivative of phencyclidine (PCP).*
- B) *It is FDA-approved for the treatment of opioid use disorder.*
- C) *Its metabolism is purportedly mediated by the p450 cytochrome enzyme CY2D6.*
- D) *It is easiest to obtain in the United States, and travel from other countries to obtain treatment is common.*

**13. Which of the following statements regarding kratom products in the United States is TRUE?**
- A) *All kratom products are considered Schedule I drugs.*
- B) *The products are typically freeze-dried leaves, concentrated extracts, or liquid "energy shots."*
- C) *Products marketed in the United States have been tested for purity and uniform concentration.*
- D) *While kratom products are available locally in smoke and "head" shops, they cannot be legally purchased over the Internet.*

**14. Mescaline toxicity can result in**
- A) *bradycardia.*
- B) *hypotension.*
- C) *hypothermia.*
- D) *respiratory depression.*

**15. Nitrous oxide has been demonstrated to improve the condition of individuals with**
- A) *PTSD.*
- B) *psychosis.*
- C) *treatment-resistant depression.*
- D) *attention deficit Hyperactivity disorder.*

**16. The most common adverse effect of ayahuasca is**
- A) *flashbacks.*
- B) *severe headache.*
- C) *nausea and vomiting.*
- D) *respiratory depression.*

**17. Research indicates that a modest dose of psilocybin given to patients with terminal cancer under the supervision of trained therapists can improve**
- A) *prognosis.*
- B) *life expectancy.*
- C) *mood and quality of life.*
- D) *tumor size and associated pain.*

**18. Which of the following psychedelics has been studied for the treatment of social anxiety in persons with autism?**
- A) *MDMA*
- B) *Ibogaine*
- C) *Mescaline*
- D) *Psilocybin*

**19. The goal of electroconvulsive therapy (ECT) is to**
- A) *stimulate the prefrontal cortex.*
- B) *provide a competing traumatic experience.*
- C) *induce a seizure through applied electric shocks.*
- D) *induce the creation of new dendrites in the brain.*

**20. Deep brain stimulation**
- A) *is dangerous and potentially painful.*
- B) *is the subject of intense research for the treatment of eating disorders.*
- C) *has been proven effective in amelioration of severe depression in large randomized controlled trials.*
- D) *involves the permanent implantation of electrodes that send regular and continuous electrical impulses to stimulate a specific part of the brain.*

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.***

# Osteoarthritis

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

***Audience***

This course is designed for physicians, physician assistants, nurses, and other healthcare professionals involved in the care of patients with osteoarthritis.

***Course Objective***

The high prevalence of osteoarthritis and its substantial burden at both the individual and healthcare system levels demands sound knowledge and clinical skills in diagnosing and managing the disease. The purpose of this course is to provide healthcare professionals with the information necessary to adequately assess osteoarthritis symptoms, treat osteoarthritis patients based on evidence-based guidelines, and appropriately refer to specialists.

***Learning Objectives***

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

1. Discuss the prevalence of osteoarthritis in the context of demographic variables.
2. Describe what is known about the etiology and pathogenesis of osteoarthritis.
3. List the risk factors for the development of osteoarthritis.
4. Identify the diagnostic criteria for osteoarthritis at various anatomic sites.
5. Describe the roles of radiography and patient-related factors in the diagnosis of osteoarthritis.
6. Recommend lifestyle changes and education strategies that should be incorporated into the osteoarthritis treatment plan.
7. Apply evidence-based guidelines for the appropriate use of oral and topical analgesics to manage osteoarthritis symptoms.
8. Analyze the appropriateness of intra-articular medications for the treatment of osteoarthritis.
9. Discuss alternative therapies that lack evidence to support their routine use in the management of osteoarthritis.
10. Identify operative procedures used to manage osteoarthritis.

***Faculty***

**Lori L. Alexander, MTPW, ELS, MWC**, is President of Editorial Rx, Inc., which provides medical writing and editing services on a wide variety of clinical topics and in a range of media. A medical writer and editor for more than 30 years, Ms. Alexander has written for both professional and lay audiences, with a focus on continuing education materials, medical meeting coverage, and educational resources for patients. She is the Editor Emeritus of the *American Medical Writers Association (AMWA) Journal*, the peer-review journal representing the largest association of medical communicators in the United States. Ms. Alexander earned a Master's degree in technical and professional writing, with a concentration in medical writing, at Northeastern University, Boston. She has also earned certification as a life sciences editor and as a medical writer.

***Faculty Disclosure***

Contributing faculty, Lori L. Alexander, MTPW, ELS, MWC, 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.

Through an agreement between the Accreditation Council for Continuing Medical Education and the Royal College of Physicians and Surgeons of Canada, medical practitioners participating in the Royal College MOC Program may record completion of accredited activities registered under the ACCME's "CME in Support of MOC" program in Section 3 of the Royal College's MOC Program.

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## INTRODUCTION

Many conditions comprise musculoskeletal diseases, but osteoarthritis is by far the most common joint disorder, particularly osteoarthritis of the knee. The disease exacts a high cost in terms of pain and decreased function. Osteoarthritis is a leading cause of activity limitation and absenteeism among working-age adults and is associated with a significant decline in function among older individuals. The toll of osteoarthritis on the healthcare system is also great, with high rates of physician office visits and hospitalizations, and the burden of the disease is expected to increase.

Osteoarthritis is a complex disease. Its etiology is not completely understood, and its risk factors and clinical and radiographic presentation vary according to the joint site. This complexity creates a challenge for diagnosis and management. Although diagnostic criteria exist, diagnosis can be difficult for a variety of reasons, most notably, a low sensitivity of radiographs in detecting early osteoarthritic changes and the lack of correlation between radiographic evidence of disease and symptoms. As no curative therapy for osteoarthritis is currently available, management is focused on decreasing pain and increasing function. The great range in treatment options has made it difficult to determine which ones are most effective; more than 50 treatment modalities have been addressed in 23 guidelines for the management of knee and hip osteoarthritis alone. Adding to the challenge of selecting appropriate therapy is evolving evidence on the efficacy of specific options; systematic reviews, meta-analyses, and randomized controlled clinical trials have demonstrated that many commonly used treatment options for osteoarthritis offer limited or no benefit. This course addresses osteoarthritis of the most commonly involved joints (knee, hip, and hand), providing important details on risk factors, diagnosis, and the most current evidence-based recommendations for treatment.

## SCOPE OF THE PROBLEM

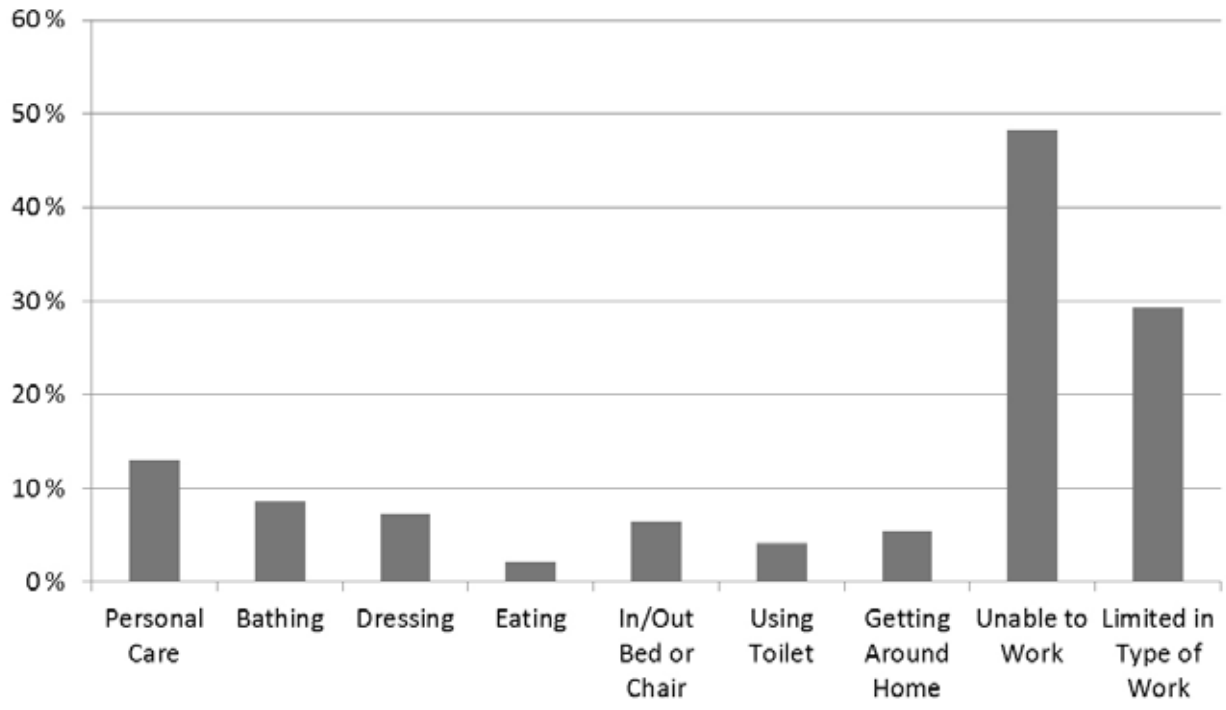
Arthritis and musculoskeletal diseases were, and continue to be, the leading cause of activity limitation across all age groups in the United States (***Figure 1***) [1; 2; 3]. Approximately 55.4 million adults in the United States have diagnosed arthritis [4]. Osteoarthritis is by far the most common type of arthritis and is one of the leading chronic diseases in the United States, affecting an estimated 30.8 million adults and nearly 50% of people by 85 years of age [4; 5; 6; 7]. In addition, the prevalence of the condition is rapidly increasing; from 1997 to 2009, the prevalence increased 95% overall and 151% among individuals 45 to 64 years of age and continues to increase concurrent with the aging population and obesity epidemic [4; 8]. By 2040, it is projected that 78 million individuals (26% of the United States population) will have diagnosed arthritis [6]. It is the leading cause of chronic disability in individuals older than 70 years [9]. This exponential rise is unique to osteoarthritis, as there have not been similar increases in the prevalence of other types of joint diseases [4; 8].

Osteoarthritis exacts a cost in terms of pain, limited mobility, and decreased function among a wide range of individuals. Among working-age individuals, arthritis is a leading cause of activity limitation and absenteeism [7; 10]. For the older population, osteoarthritis is associated with a significant decline in function and causes a higher rate of disability than any other chronic condition, including cardiovascular disease [11; 12].

The toll of osteoarthritis on the healthcare system is also high. Arthritis (all types) is a leading reason for physician office visits, and hospitalizations for osteoarthritis increased nearly 70% between 2007 and 2018 [8; 13]. It has been noted that the increase in hospitalizations is primarily related to higher rates of joint replacement; specifically, a significant increase in knee and hip replacement surgery [1; 14]. An estimated 704,000 hospitalizations in 2012 were due to osteoarthritis-related knee replacement surgery (compared with 416,000 in 2004), and an estimated 296,000 hospitalizations were for osteoarthritis-related first-time hip replacement in 2012 (compared with 172,000 in 2003) [15]. Osteoarthritis is also a substantial economic burden; according to the Medical Expenditure Panel Survey for the years 1996 – 2005, osteoarthritis raised aggregate annual medical care expenditures by $185.5 billion ($149.4 billion in insurer expenditures and $36.1 billion in out-of-pocket expenditures) [16; 17]. Data from the Healthcare Cost and Utilization Project (HCUP) indicate that osteoarthritis was the second most expensive condition billed to Medicare ($11.3 billion) and first most expensive billed to private insurance ($4.6 billion) in 2017 [18]. For total knee arthroplasty alone, Medicare was billed $3.5 billion, the program's largest expenditure for a single procedure [4]. Between 2008 and 2011, earning losses due to osteoarthritis cost an estimated $80 billion per year. A 2012 study showed that osteoarthritis was the most frequent cause of work loss, affecting more than 20 million individuals and costing the U.S. economy more than $100 billion annually [4].The burden of osteoarthritis is expected to increase as the population grows older and lives longer, especially given the high rate of obesity [1; 19].

The high prevalence of osteoarthritis and its substantial burden at both the individual and healthcare system levels demand that clinicians have sound knowledge and clinical skills in diagnosing and managing the disease. However, several studies have shown that medical education in musculoskeletal disorders is inadequate, and competency examinations and surveys have shown that medical students and residents lack the necessary knowledge and clinical confidence in this field [20; 21; 22; 23; 24]. As a result, the Association of American Medical Schools has made recommendations for improving the undergraduate medical school curriculum on musculoskeletal diseases [25].

**SELF-REPORTED ACTIVITIES OF DAILY LIVING (ADL) WITH PERFORMANCE LIMITATIONS DUE TO MUSCULOSKELETAL CONDITIONS—UNITED STATES, 2015**




*Source: [3]* *Figure 1*

Inadequate education and training in musculoskeletal diseases has left many primary care physicians—often the first ones to evaluate individuals with signs and symptoms of osteoarthritis—feeling ill-equipped to manage the disease [22; 26; 27]. This course is designed to help fill this substantial educational gap by providing an overview of the prevalence and natural history of osteoarthritis, details on risk factors for the disease, and a discussion of the evidence base for a wide range of medical treatment options. Because surgical treatment options are not within the purview of primary care physicians, these options will be addressed briefly. The primary focus of this course is osteoarthritis of the knee, hip, and hand, as disease at these joints has the greatest clinical impact and is associated with the greatest public health burden [1; 19]. In addition, most of the literature on osteoarthritis focuses on these joints. Osteoarthritis of other joints—primarily the shoulder, elbow, and ankle—is discussed as appropriate.

## OVERVIEW OF OSTEOARTHRITIS

As noted, osteoarthritis develops most frequently in the knee, hip, and hand. Although pain in the lower back and the neck are the most frequently occurring musculoskeletal conditions and are the leading cause of functional limitation and work absences, the etiology of back and neck pain is often unclear, with many cases involving muscles and ligaments rather than osteoarthritic changes [5; 28; 29].

Osteoarthritis is classified as primary or secondary. The cause of primary osteoarthritis is idiopathic; no abnormality is the cause of changes in the joint [9]. Secondary osteoarthritis is the result of a known cause, most often trauma/injury or systemic diseases. Secondary osteoarthritis is most often found in the shoulder, elbow, and ankle and is more likely to become clinically apparent at a younger age than primary osteoarthritis [9; 30; 31; 32]. A population-based study showed that secondary osteoarthritis related to trauma accounts for approximately 12% of the overall prevalence of symptomatic osteoarthritis of the knee, hip, or ankle [33]. Injuries sustained in sports activities comprise a large portion of post-traumatic osteoarthritis [34]. A wide variety of systemic diseases have been identified

| SYSTEMIC CONDITIONS ASSOCIATED WITH SECONDARY OSTEOARTHRITIS | |
|---|---|
| **Disease** | **Joint Affected** |
| **Metabolic Diseases** | |
| Hemochromatosis | Knee, hip, ankle |
| Gaucher disease | Knee, hip |
| Hemoglobinopathies (e.g., sickle cell disease and thalassemia) | Knee, hip |
| Wilson disease (hepatolenticular degeneration) | Knee, hip |
| Ochronosis | Knee, hip |
| Ehlers-Danlos syndrome (and other joint hypermobility) | Knee, hip |
| Avascular necrosis | Hip, ankle |
| **Endocrine Diseases** | |
| Acromegaly | Knee, hip |
| Hypothyroidism (severe stages) | Knee, hip |
| Hyperparathyroidism | Knee, hip |
| **Bone Dysplasias** | |
| Multiple epiphyseal dysplasia | Knee, hip |
| Spondyloepiphyseal dysplasia | Knee, hip |
| Progressive hereditary arthro-ophthalmopathy (Stickler syndrome) | Knee, hip |
| Osteo-onychodystrophy (nail-patella syndrome) | Knee, hip |
| Epiphyses-related conditions | Knee, hip |
| Osteochondritis dissecans | Elbow, ankle |
| **Calcium Crystal Deposition Diseases** | |
| Calcium pyrophosphate deposition disease | Knee, hip, MCP joint (especially middle and index fingers) |
| Apatite crystal deposition disease | Knee, hip |
| Gout | Hip |
| **Other Systemic Diseases** | |
| Neuropathic arthropathy (Charcot joints) | Knee, hip |
| Paget disease (osteitis deformans) | Knee, hip |
| Osteopetrosis | Knee, hip |
| Chondrocalcinosis | Hip |
| MCP = metacarpophalangeal. | |
| *Source: [9; 30; 36; 37; 38]* | *Table 1* |

as frequent causes of secondary osteoarthritis; these conditions include metabolic diseases, endocrine disorders, bone dysplasias, and crystal deposition diseases (***Table 1***) [9; 35].

Research has shown that the symptoms of osteoarthritis do not correlate well with its radiographic evidence [19; 39; 40; 41]. According to a systematic literature review, radiographic evidence of osteoarthritis is found in 15% to 76% of individuals with pain, and 15% to 81% of individuals with radiographic evidence of disease have pain [39]. An estimated 40% of individuals with structural changes on radiographs are asymptomatic [39; 40]. In addition, many individuals have joint-related symptoms and no radiographic evidence [5; 9]. As a result of this discordance, the disease is defined as either radiographic (evidence on imaging studies) or symptomatic (frequent pain in a joint plus radiographic evidence of osteoarthritis in that joint) [42]. Total joint replacement is used as a surrogate measure of symptomatic end-stage osteoarthritis, as the procedure is the option chosen when nonoperative measures have failed to manage pain and improve function and mobility.

## PREVALENCE

Some large-scale, population-based studies have been used to determine the prevalence of osteoarthritis overall and within demographic subgroups (by age, gender, and race/ethnicity) and according to joint site. Among the most-often cited sources are the Framingham Osteoarthritis Study and the Johnston County Osteoarthritis Project. The Framingham Osteoarthritis Study involved a cohort of approximately 2,400 adults (26 years of age and older) from the Framingham Heart Study, and osteoarthritis of the knee and hand were evaluated [43; 44]. The Johnston County Osteoarthritis Project was designed to compare the prevalence of knee and hip osteoarthritis in approximately 3,000 White and Black men and women (45 years of age and older) in a rural county in North Carolina [45; 46].

In addition, information on the prevalence of osteoarthritis has been gathered through several national surveys, such as the National Health Interview Survey (NHIS), the National Health and Nutrition Examination Survey (NHANES), the National Hospital Discharge Survey, and the Ambulatory Care Survey. The NHIS is conducted among a cross-section of adults (18 years of age and older) each year. NHANES involves a nationally representative sample of about 5,000 persons each year who are interviewed and physically examined. The National Hospital Discharge Survey and the Ambulatory Care Survey capture the number of specific diagnoses for inpatient stays and outpatient visits, respectively.

Determining the prevalence of osteoarthritis is challenging for several reasons. First, few epidemiologic data are available for specific types of arthritis or joint-specific osteoarthritis, and the questions in surveys such as NHIS and NHANES refer to a single category of arthritis. Given that osteoarthritis has been shown to represent an overwhelming proportion of all types of arthritis, it seems reasonable to expect that osteoarthritis would account for most of the data gathered in a broad "arthritis" category [5]. In addition, although survey questions specifically refer to "doctor-diagnosed" arthritis, survey data have limitations, as they represent self-reports of the disease. Further complicating the situation are the differences across studies in how osteoarthritis is defined—radiographic or symptomatic—and in how radiographic changes are defined—mild or moderate/severe. Also problematic is the lack of correlation between radiographic evidence of osteoarthritis and symptoms and the high number of individuals who do not seek medical care for joint-related symptoms.

Several studies point to a high—and increasing—prevalence of arthritis. Data from the 2013–2015 NHIS showed a prevalence of doctor-diagnosed arthritis of 22.7% in adults, a rate similar to the 21% reported in a later analysis of combined data from the 2002, 2003, and 2006 NHIS [6; 47; 48]. These rates represent a substantial increase over previous decades; according to the 1971–1975 NHANES (NHANES I), the prevalence of osteoarthritis was approximately 12% among adults [49]. In the NHIS, the prevalence of arthritis varied substantially with age, ranging from 13.8% for those 18 to 44 years of age to 42.7% for those 65 years of age and older [50].

Data on hospitalizations indicate an increase in the prevalence of arthritis. The number of hospital stays with a principal diagnosis of arthritis increased from 921,000 in 2009 to 1.1 million in 2018 [8; 51]. Osteoarthritis moved from the sixth leading principal diagnosis in 1990 to the second leading diagnosis in 2018 [1; 51; 52]. Although the number of physician office visits for arthritis decreased slightly from 1996 to 2014, arthritis was the third-leading chronic condition diagnosis for visits in 2018, accounting for 11.5% of all adult (18 years of age and older) visits (***Figure 2***) [53].

Data show that the prevalence of arthritis (and osteoarthritis specifically) can differ substantially according to age, gender, and race/ethnicity.

### Age

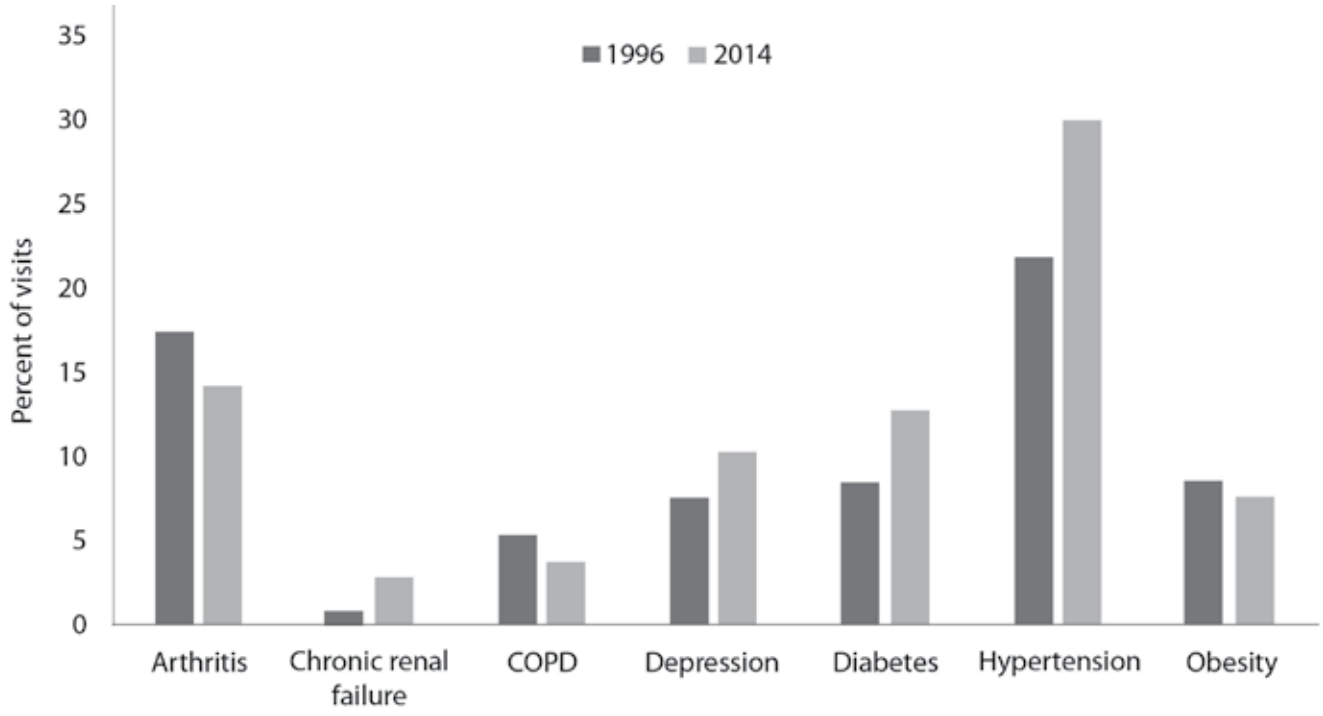
The prevalence of all types of arthritis increases with age. According to a CDC analysis of data from the 2016–2018 NHIS, the prevalence was 7.1% for individuals 18 to 44 years of age, 30.5% for individuals 45 to 64 years of age, and 50.4% for individuals 65 years of age and older [50].

The prevalence of osteoarthritis, specifically, also increases according to age, with the highest prevalence among those 65 years of age and older [50]. (The lower rate of hospitalization for osteoarthritis among individuals 85 years of age and older is more a reflection of lower rates of arthroplasty than of actual frequency of osteoarthritis.) The increases in osteoarthritis over time follow the same age-related pattern. Between 1997 and 2009, the prevalence of osteoarthritis increased 151% among individuals 45 to 64 years of age and 58% among individuals 65 to 84 years of age [8]. Between 2009 and 2013, the prevalence of osteoarthritis increased 42% among individuals 45 to 64 years of age and 25% among individuals 65 to 84 years of age [8; 54].

The increased prevalence of radiographic and symptomatic osteoarthritis among older individuals is found across all joints. In the Nurses' Health Study, the risk of hip replacement for women 70 years of age or older was nine times greater than for women younger than 55 years of age [54]. Similarly, in the NHANES III, the prevalence of radiographic knee osteoarthritis increased with age, from a low of 17.7% for the 60 to 64-year age-group to 26.0% for the 80 years and older age-group [55]. The prevalence of hand osteoarthritis also increases significantly with age, and a review of the literature (1950–2009) demonstrated that the prevalence can reach 80% in the older population [56; 57].

**OFFICE VISITS FOR SELECTED CHRONIC CONDITIONS BY ADULTS IN THE UNITED STATES**




*Source: [53]* *Figure 2*

Data on the age at the time of diagnosis of osteoarthritis at other joints are limited. However, studies have indicated a younger age at the time of clinical presentation of elbow osteoarthritis (approximately 50 years) and ankle osteoarthritis (43 to 58 years) [32; 58].

**Gender**

The overall prevalence of arthritis (all types) has consistently been higher among women than men [50]. According to a CDC analysis of NHIS data from 2016–2018, the prevalence of arthritis was approximately 24.2% for women compared with 18.5% for men [50]. With respect to osteoarthritis specifically, women accounted for approximately 59% of hospitalizations for osteoarthritis in 2013, a proportion that has been essentially the same since 1997 [59; 60]. One exception to this female predominance relates to age; within the population of individuals younger than 50 years of age, osteoarthritis is more common in men, a difference that has been attributed to a higher rate of osteoarthritis secondary to joint injury [61]. Because osteoarthritis is overall more prevalent in women and women use healthcare resources to a greater degree than men, the economic burden of osteoarthritis is disproportionately high among women. The total expenditures related to osteoarthritis among women account for nearly two-thirds of the increased cost, or $118 billion [17].

Studies have also provided information regarding gender differences in the prevalence of osteoarthritis according to the affected joint. These studies have shown that symptomatic knee, hip, and hand osteoarthritis are more prevalent among women than among men, with the greatest difference related to knee osteoarthritis (***Table 2***) [45; 46; 56; 62]. Again, there is one exception to female predominance: osteoarthritis of the elbow, which has a male-to-female ratio of approximately 4:1 [58]. This gender difference is likely due to the predominance of elbow osteoarthritis among individuals who have an occupation involving strenuous manual labor [58]. Information on gender differences in osteoarthritis at other joint sites is lacking.

***Knee***

Osteoarthritis of the knee is estimated to account for 83% of the total number of osteoarthritis cases [2]. Using data from NHANES III, Dillon et al. found that symptomatic radiographic knee osteoarthritis did not differ by gender but that the prevalence of asymptomatic radiographic osteoarthritis was greater among women (42% vs. 31%) [62]. In addition, there were significantly more moderate-to-severe osteoarthritic changes among women (13% vs. 17%) [62]. In the Johnston County Osteoarthritis Project, symptoms, radiographic knee osteoarthritis (mild and moderate-to-severe), and symptomatic

| COMPARISON OF JOINT-SPECIFIC OSTEOARTHRITIS IN MEN AND WOMEN[a] | | | | | | |
|---|---|---|---|---|---|---|
| Joint | Radiographic Osteoarthritis[b] | | | Symptomatic Osteoarthritis | | |
| | Overall | Women | Men | Overall | Women | Men |
| Knee | 0.9% | 1.2% | 0.4% | 12.1% | 13.6% | 10.0% |
| Hip | 2.5% | 2.5% | 2.6% | 9.7% | 11.1% | 8.3% |
| Hand | 7.3% | 9.5% | 4.8% | 8.0% | 8.9% | 6.7% |

[a]The prevalence of knee and hand osteoarthritis was determined in adults 60 years of age and older, and the prevalence of hip osteoarthritis was determined in adults 55 years of age and older.
[b]Radiographic osteoarthritis defined as evidence of moderate-to-severe changes.

*Source: [45; 46; 56; 62]* *Table 2*

knee osteoarthritis were all more prevalent among women than men [45]. Data from the Global Burden of Disease Study 2010 found that the prevalence of knee osteoarthritis in women is nearly twice that of men worldwide [63]. Results of a 2020 study indicate that the worldwide prevalence of knee osteoarthritis in women is more than two-thirds higher than that of men [64].

### *Hip*

In the Johnston County Osteoarthritis study, hip symptoms, mild radiographic osteoarthritis, and symptomatic osteoarthritis were more prevalent among women than men. However, the prevalence of moderate-to-severe radiographic osteoarthritis was similar (2.6% for men vs. 2.5% for women) [46].

### *Hand*

The data on gender differences for osteoarthritis of the hand have been conflicting. Of 1,041 men and women (71 to 100 years of age), the prevalence of symptomatic hand osteoarthritis was twice as high among women in the Framingham Osteoarthritis Study (26% vs. 13%), but NHANES III data showed that the prevalence of symptomatic hand osteoarthritis was similar among men and women [44; 56]. The difference may be due to the older age of individuals in the Framingham study, as the prevalence of hand osteoarthritis increases significantly with age [56]. A review of the literature (1950–2009) supports a gender difference in the prevalence of osteoarthritis of the hand [57].

## Race/Ethnicity

Data from 2016–2018 NHIS showed a higher prevalence of arthritis (all types) in the non-Hispanic White population (23.2%) compared with the non-Hispanic Black (21.8%), Hispanic (16.4%), and Asian/Pacific Islander populations (12.2%) [50]. In contrast, the prevalence was higher for the American Indian/Alaska Native population (26.8%) [50].

### *Knee*

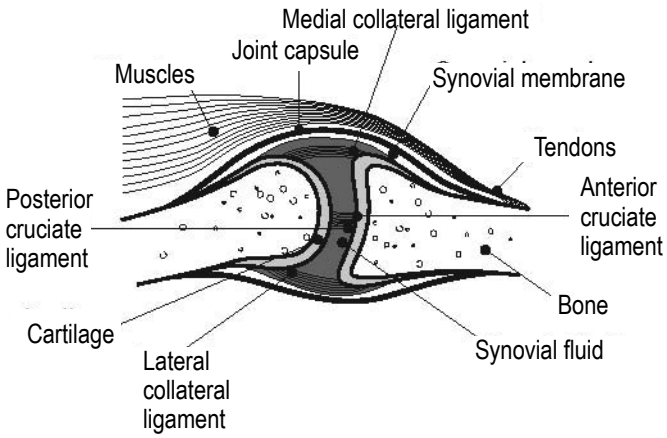
Studies have consistently shown that osteoarthritis of the knee is more prevalent in the Black population than the White population. Multivariable analysis of data from NHANES III showed significantly higher odds of radiographic knee osteoarthritis (Kellgren-Lawrence grade 2 or higher) among non-Hispanic Black participants (52%) compared with White (36%) or Mexican American (38%) participants [62; 65]. Although the findings of the Johnston County Osteoarthritis Project also demonstrated that knee-related symptoms, radiographic knee osteoarthritis (mild), and symptomatic knee osteoarthritis were all more prevalent among Black individuals than White individuals, the difference was slight. However, the prevalence of moderate-to-severe radiographic osteoarthritis was significantly greater for both men and women in the Black population (11% vs. 5% for Black vs. White men and 16% vs. 8% for Black vs. White women) [45]. A study of more than 1,000 premenopausal and perimenopausal women demonstrated that early osteoarthritis changes were more prevalent in Black women than White women (23% vs. 9%) [66]. The prevalence of knee osteoarthritis has also been found to be higher in the Chinese population than in the White population [67].

### *Hip*

In the Johnston County Osteoarthritis Project, the greatest racial/ethnic difference was found for mild radiographic hip osteoarthritis among men (23.8% vs. 33.2% for White vs. Black men) [46]. There were also racial differences among men and women for symptomatic hip osteoarthritis (7.6% vs. 11.7% for White vs. Black men, and 10.8% vs. 12.2% for White vs. Black women) [46]. Among women, the prevalence of moderate-to-severe radiographic hip osteoarthritis was higher for the Black population (2.3% vs. 3.5%) [46]. A subsequent study indicated that the radiographic features and patterns of hip osteoarthritis differed according to race and gender, which suggests that anatomic and/or development variations in the joint may contribute to differences [68]. Hip osteoarthritis has been found to be less prevalent among Chinese individuals than among White individuals [67].

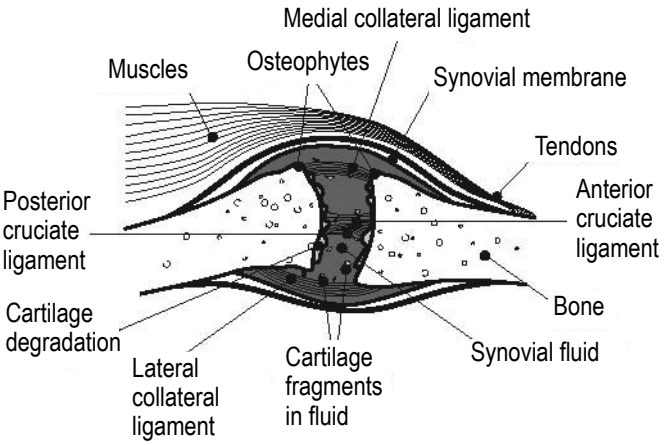
  

**A HEALTHY JOINT**




*Source: Reprinted from National Institutes of Health. Osteoarthritis. Bethesda, MD: National Institutes of Health; 2006.* *Figure 3*

**A JOINT WITH SEVERE OSTEOARTHRITIS**




*Source: Reprinted from National Institutes of Health. Osteoarthritis. Bethesda, MD: National Institutes of Health; 2006.* *Figure 4*

### *Hand*

In a study of more than 1,000 younger women (premenopausal and perimenopausal), the prevalence of hand osteoarthritis was higher among Black women (26%) than among White women (19%), and the specific hand joints affected differed between the two groups [66]. However, NHANES III data indicated that symptomatic hand osteoarthritis occurred less frequently among non-Hispanic Black individuals than White individuals [56]. Research has also indicated that hand osteoarthritis is less common in the Chinese population than in the White population [67; 68].

## PATHOGENESIS

Historically, osteoarthritis has been considered to be a disease of articular cartilage, but research has indicated that the condition involves the entire joint organ [9; 69; 70]. The loss of articular cartilage has been thought to be the primary change, but a combination of cellular changes and biomechanical stresses causes several secondary changes, including subchondral bone remodeling; the formation of osteophytes; the development of bone marrow lesions; changes in the synovium, joint capsule, ligaments, and periarticular muscles; and meniscal tears and extrusion (***Figure 3*** and ***Figure 4***) [19; 71; 72; 73; 74]. These changes lead to structural and functional changes in the joint, causing pain, disability, and psychologic distress [70].

| DIFFERENCES BETWEEN OSTEOARTHRITIC JOINTS AND AGING JOINTS | | |
|---|---|---|
| **Feature** | **Osteoarthritic Joint** | **Aging Joint** |
| Fibrillation in cartilage | Primarily weight-bearing joints | Nonweight-bearing joints |
| Cartilage mass | Hypertrophy, erosion | No change |
| Water content of cartilage | Edema (early stage) | No change or dehydration |
| Cell activity | Increased activity and proliferation | Reduced |
| Synovium | Mild focal superficial inflammation | Atrophy |
| Bone changes | Subchondral bone remodeling | Osteopenia |
| *Source: [72]* | | *Table 3* |

**Early Development of Osteoarthritis**

Normal adult articular cartilage is made up of extracellular matrix (approximately 98% to 99%) and chondrocytes (1% to 2%) [75]. The chondrocytes secrete enzymes and cytokines that help regulate the normal cycle of degradation and repair of articular cartilage by inhibiting the production of proteoglycans and collagen, the two major components of the extracellular matrix [75]. Damage to the extracellular matrix interferes with its ability to bind or exclude water, resulting in edema and subsequent softening of the cartilage and expansion of the matrix, which makes the matrix vulnerable to further injury and breakdown of its components [9; 76; 77; 78].

Among the enzymes stimulated by chondrocytes are matrix metalloproteinases (e.g., collagenase, stromelysin, and gelatinase) and other proteinases (e.g., cathepsin and tissue plasminogen activator). Interleukin-1 (IL-1) is the cytokine that has been identified as playing an important role in promoting the synthesis of degradative enzymes, and tumor necrosis factor-alpha and IL-6 have been found to work synergistically with IL-1. Inhibitors of these enzymes and cytokines, such as tissue inhibitor of metalloproteinase (TIMP) and plasminogen activator inhibitor-7 (PAI-7), help stimulate a repair process by keeping degradation in check. In addition, polypeptides, such as insulin-like growth factor-1 (IGF-1) and transforming growth factor-beta (TGF-beta), stimulate chondrocytes to synthesize proteoglycans. When chondrocyte function is lost, the balance between degradation and repair is lost, resulting in damage to the articular cartilage [79].

There are some indications that the early structural changes of osteoarthritis (such as bone marrow lesions and cartilage defects) may be reversible, especially among younger individuals [72; 74]. However, it is difficult to detect early changes, given the high percentage of individuals who are asymptomatic during the early development of osteoarthritis [70]. Still, the potential reversibility sets up early changes as a target for disease-modifying interventions, and research is being directed in this area.

**Damage to Other Joint Structures**

As damage occurs to the articular cartilage, fragments of cartilage may break off and enter into the joint capsule, where they can damage the synovial lining of the joint and interfere with proper joint function. Continued erosion of cartilage results in narrowing of the joint space, with the potential for bone-to-bone contact. Eburnation, or the formation of a new articulating surface from subchondral bone, may occur. Bone remodeling may also occur in the subchondral bone, which may cause overgrowth of bone at the edges of the joint. These osteophytes usually develop in the nonweight-bearing area of a joint. In osteoarthritis of the distal interphalangeal joints, these osteophytes are dorsolateral swellings referred to as Heberden's nodes [36].

**Evolving Definition**

The lack of clarity about the etiology of osteoarthritis is further complicated by the terminology used to refer to the disease. The term "osteoarthritis" implies an inflammatory process, but inflammation is not a hallmark characteristic of the disease; if inflammation is involved, it is usually mild and affects only the synovium and periarticular tissues [79]. Alternative terms that have been suggested include "osteoarthrosis" and "degenerative joint disease," but neither term is completely satisfactory. The former is vague, and although the latter term is more accurate, it implies a process that naturally occurs with aging, and many differences between the osteoarthritic joint and the aging joint have been identified (***Table 3***) [9; 72].

The definition and natural history of osteoarthritis continues to evolve as research provides new information. Some researchers have now posited that an inflammatory process is present during the early development of osteoarthritis, with a suggestion that osteoarthritis has a biochemical and inflammatory profile similar to that of metabolic syndrome [74; 80]. Another study providing evidence of a different natural history of osteoarthritis indicated that structural changes precede articular damage. In that study, the results of magnetic resonance imaging (MRI) of healthy knees and knees with early osteoarthritis suggested that such changes as subchondral

bone expansion, bone marrow lesions, and meniscal tears and extrusion lead to defects in the articular cartilage, which may or may not subsequently result in loss of articular cartilage and radiographic evidence of osteoarthritis [74].

**Etiology of Pain**

The cause of osteoarthritis-related pain is not well understood. Because articular cartilage is aneural and avascular, degradation of cartilage, a primary characteristic of osteoarthritis, is not likely to be the direct source of pain, stiffness, or other typical symptoms [70]. The probable sources of pain, therefore, are other tissues in the joint structure that are richly innervated, such as the subchondral bone, periosteum, periarticular ligaments, periarticular muscle, synovium, and joint capsule [9; 70]. Pain is most likely generated by several factors, and the predominant source of pain has been unclear, as the severity of osteoarthritis on radiographs does not correspond to the degree of pain [70]. However, the improved imaging of the joint provided by MRI has allowed researchers to explore the source of osteoarthritis-related pain, and studies have shown that bone marrow lesions, synovitis/effusion, subarticular bone attrition, osteophytes in the patellofemoral compartment, and meniscal tears are strongly associated with severity of pain in knee osteoarthritis [9; 41; 81; 82; 83]. The evidence has been strongest for bone marrow lesions and synovitis, and the association is greater for pain on weight-bearing (compared with nonweight-bearing) joints [83]. Psychologic and social factors also play an important role in osteoarthritis-related pain [9; 70].

**Osteoarthritis as Distinct Entities According to Joint**

There is substantial heterogeneity in osteoarthritis across anatomic sites with regard to risk factors, clinical features, and outcomes, which has drawn some researchers to conclude that osteoarthritis of different joints are distinct clinical entities [84; 85]. Some examples to support the concept of distinct disease entities include [31; 32; 36; 86]:

- Primary osteoarthritis of the knee is more common than secondary osteoarthritis, but primary osteoarthritis of the ankle is rare, with the disease at that joint occurring more often after trauma (e.g., fracture or ligamentous injury).
- Overweight/obesity has been identified as the most common risk factor with knee osteoarthritis, but mechanical overuse is the primary predisposing factor for hand osteoarthritis.
- Erosion of articular cartilage and narrowing of the joint space are hallmark characteristics of knee and hip osteoarthritis, but articular cartilage is relatively preserved. There is no joint space narrowing in primary osteoarthritis of the elbow.

Osteoarthritis of more than one joint may be a distinct disease in which a genetic predisposition plays a more important role than biomechanical factors [84].

## RISK FACTORS

The risk factors for osteoarthritis include several modifiable as well as nonmodifiable factors (***Table 4***) [9; 30; 32; 36; 37; 38; 57; 87; 88; 89]. Secondary osteoarthritis can also develop as a result of a systemic disease, as noted earlier [70]. Some of the same risk factors for the development of osteoarthritis are also factors that have been noted to increase the risk of disease progression.

As discussed, age, gender, and race/ethnicity influence the development of osteoarthritis at many joint sites. Genetic predisposition is another nonmodifiable risk factor. Among the modifiable risk factors, the greatest contributor to development of the disease is overweight/obesity. Previous trauma/joint injury and specific sporting or occupational activities are other important risk factors. The potential contribution of many other factors is still being explored.

### GENETIC PREDISPOSITION

Studies have indicated that there may be a genetic factor to the development of osteoarthritis, and the familial risk factor for osteoarthritis of the knee, hip, and hand has ranged from 27% to 60% [35; 57; 84]. It is thought that most genes related to osteoarthritis affect the development of the disease at any joint but that specific genes may also be involved at specific joints [35; 84]. Over the past several years, a candidate gene study and several genome-wide association studies have collectively established 15 loci associated with knee or hip osteoarthritis that have been replicated with genome-wide significance, providing further evidence of joint-specific effects in osteoarthritis [19; 84; 85; 90; 91; 92; 93; 94]. In 2019, researchers performed a genome-wide association study with more than 77,000 participants and identified 64 loci, 52 of them being novel. Of these 64 loci, therapeutics are currently available or in clinical trials for 10 of the effector genes, making them a future prospect for effective treatment of osteoporosis [95]. Despite the increased reports of potential risk loci for osteoarthritis, some research indicates that epigenetic changes may have a role in the pathogenesis of osteoarthritis [96].

### OVERWEIGHT/OBESITY

Clinical studies have long demonstrated that the risk of osteoarthritis is higher for individuals who are overweight or obese, and obesity has been referred to as the most important modifiable risk factor for severe osteoarthritis of the knee and, to a lesser extent, of the hips [9; 97; 98; 99]. In a meta-analysis, those who were obese or overweight were nearly three times as likely to report osteoarthritis of the knee [100]. Overweight as a risk factor is thought to be related to the increased load on weight-bearing joints; however, some studies have indicated an association between obesity and osteoarthritis of the hand and shoulder, which suggests factors other than joint overload [30; 36; 57]. Factors that have been proposed are a metabolic

| RISK FACTORS FOR OSTEOARTHRITIS | |
|---|---|
| **Risk Factor** | **Joint** |
| **Nonmodifiable** | |
| Age | Knee, hip, hand |
| Gender | Knee, hip, hand (women); elbow, cervical spine (men) |
| Race/ethnicity | Knee, hip, hand |
| Genetic predisposition | Knee, hip, hand |
| **Modifiable** | |
| Overweight/Obesity | Knee, hip, hand, shoulder |
| Previous trauma, joint injury | Ankle, glenohumeral joint, knee, hip, hand, wrist |
| High-impact sports | Knee, hip |
| Occupational activities | Knee, hip, elbow (manual labor, construction work)<br>Hand (clothing work, housecleaning) |
| **Other** | |
| Muscle weakness | Knee |
| Malalignment | Knee, hip, ankle |
| Bone density (high) | Knee, hip, hand |
| Vitamin C and D deficiency | Knee, hip |
| Estrogen deficiency | Knee, hip |
| Developmental deformities | Hip, glenohumeral joint, ankle |
| Joint laxity | Knee, hip, hand |
| Repeated episodes of gout or septic arthritis, or infection | Knee, hip, glenohumeral joint (infection) |
| *Source: [9; 30; 36; 37; 38; 57; 87; 88; 89]* | *Table 4* |

intermediary (such as diabetes or lipid abnormalities) or an increased production of humoral factors (produced by excess adipose tissue), which alters the metabolism of articular cartilage [9; 101].

The data on osteoarthritis and overweight have been more consistent for osteoarthritis of the knee than for disease at other joint sites, and most studies have indicated that overweight/obesity is a greater risk factor for women [38; 84; 87; 97; 101; 102; 103; 104; 105]. In the Framingham Osteoarthritis Study, there was more than a 50% decrease in the risk among women who had a loss of approximately 11 pounds or a decrease in body mass index (BMI) of 2 or more [97]. Weight gain was also associated with an increased risk for osteoarthritis, but the difference was not significant [97]. In a population-based case-control study in England (525 men and women [45 years of age and older] with primary knee osteoarthritis and 525 matched controls), the risk of osteoarthritis increased progressively with higher BMI; compared with a BMI of 24.0–24.9, the risk was 0.1 for a BMI of less than 20 and 13.6 for a BMI of 36 or greater [99].

The results of a large, prospective population-based cohort study (28,449 subjects; 17,203 women and 11,246 men) in Sweden indicated that all measures of overweight (BMI, waist circumference, waist-hip ratio, and percentage body fat) were significantly associated with a higher incidence of osteoarthritis of the knee in both men and women [103]. Across studies, the relative risk of osteoarthritis of the knee and hip has been 2 to 10 times higher for the BMI in the top quartile compared with BMI in the lowest quartile, with the risk typically higher for knee osteoarthritis than hip osteoarthritis and for women compared with men [54; 103; 106; 107; 108]. Among men, the risk for knee and hip osteoarthritis has increased with a higher BMI, even within the normal range [109]. In addition, the risk for osteoarthritis of the hip has been greater for individuals who had a high BMI beginning at a younger age [54; 106].

## EXERCISE, RECREATIONAL ACTIVITY, AND SPORTS

There is no evidence that routine, moderate exercise or leisure recreational activity increases the risk of osteoarthritis of the knee or hip [54; 84]. In a systematic review of 72 studies, a high level of physical activity was not a risk factor for osteoarthritis of the knee or hip, provided that the activity did not cause pain in the joint or predispose to trauma [110]. However, the risk for osteoarthritis appears to be associated with increasing intensity and/or duration of the activities, and there is moderate-to-strong evidence of an increased risk of osteoarthritis of the knee and hip with high-intensity, high-impact sports activities, especially when individuals are involved in such activities before the age of 50 years [87; 110; 111]. The risk of osteoarthritis of the hip and knee also has been found to be greater among individuals who participate at an elite level in sports that involve high joint loads. Overall, the risk associated with high-intensity sports is not as great as that associated with overweight or trauma [110]. With respect to other joints, the risk of osteoarthritis of the elbow has been increased after weight-lifting and throwing activities, the risk of osteoarthritis of the shoulder has been increased in association with overhead sports activities, and the risk of osteoarthritis of the spine has been higher after participation in wrestling, gymnastics, tennis, and weight-lifting [30; 31; 34].

Many researchers have theorized that injury is a stronger risk factor than sports participation itself, especially when participation continues after injury to a joint or cartilage [35; 110]. One systematic review evaluated studies that included injury, sport/physical activity, overweight/obesity, and/or occupational activity as risk factors; outcomes included osteoarthritis of the hip, knee, and/or ankle [112]. Joint injury, obesity, and occupational activity were all associated with an increased risk of osteoarthritis of the knee and hip, with joint injury identified as a significant risk factor for both knee and hip osteoarthritis. Meniscal tears and injury to a cruciate ligament have been shown to be risk factors for osteoarthritis of the knee, chronic rotator cuff tear is a risk factor for osteoarthritis of the glenohumeral joint, and injury to the ankle ligaments increases the risk for osteoarthritis of the ankle in the long-term (more than 25 years) [30; 34; 112; 113; 114].

## OCCUPATIONAL ACTIVITIES

The prevalence of osteoarthritis has been shown to be higher among individuals in occupations involving repetitive tasks that place a high load on a joint and cause fatigue in the muscles that protect the joint, although the precise nature of the biomechanical stresses that lead to osteoarthritis are unclear [84; 87; 110; 115]. Occupations that have been associated with high rates of osteoarthritis are manual labor/construction work (knee, hip, elbow, and shoulder), farming (hip), and housekeeping/housecleaning and clothing industry (hand) [30; 31; 36; 57; 62; 84; 115; 116; 117]. Specific occupational actions/activities that have been identified as risk factors for osteoarthritis of the hip or knee include heavy lifting (55 pounds or more), kneeling, squatting, walking more than 2 miles per day, climbing, jumping, and unnatural body positions [110; 115]. Occupations associated with increased risk of osteoarthritis of the hip in men include working in agriculture (including fishery, forestry, and food production), which doubles the risk. Construction, metal working, and sales as well as exposure to whole-body vibration (e.g., while driving vehicles) has been shown to increase the risk by approximately 50% to 60% [118]. Obese workers with such exposures are at additional risk of osteoarthritis of the knee [115]. Some studies have indicated that occupational workload is a more significant factor for osteoarthritis of the knee than for osteoarthritis of the hip, but little research has been conducted among female workers [119; 120]. One nationwide register-based follow-up study that included women found that construction, farming, and healthcare work (compared to office work) increases the risk of osteoarthritis of the hip and knee in both men and women, with farmers having the highest risk of osteoarthritis of the hip and construction and healthcare workers having the highest risk of osteoarthritis of the knee. The risk estimates were generally higher for men, with an exception for construction work, in which the risk estimates of osteoarthritis of the knee were similar or slightly higher for women [120].

One systematic review (25 studies) found moderate evidence for a relationship between kneeling, heavy lifting, and knee osteoarthritis; a limited number of studies indicated that the association was stronger for the combination of kneeling/squatting and heavy lifting than for kneeling/squatting or heavy lifting alone [121]. Two studies examined the interaction of obesity with kneeling/squatting and lifting [122; 123]. In both studies, squatting/kneeling and high BMI carried independent risk of knee osteoarthritis, but their combination raised the risk 5- to 15-fold. In addition, limited data indicated a relationship between climbing stairs or ladders and an increased risk for knee osteoarthritis [121]. Although most studies of occupational risk for osteoarthritis have been conducted with men, some have shown similar results among women [35].

## MUSCLE WEAKNESS

Muscle weakness as a risk factor has been primarily studied in the setting of knee osteoarthritis. Weakness of the quadriceps muscle has been found frequently among individuals with knee osteoarthritis, but it was thought to be the result of atrophy that developed as the individual tried to minimize pain in the joint [84; 124]. However, studies have indicated that weakness of this muscle may actually be a risk factor, with the weak muscle unable to appropriately distribute load across the knee joint and maintain joint stability [125; 126]. Such dysfunction may actually precede and expedite cartilage deterioration [127].

In individuals with osteoarthritis of the knee, quadriceps strength is an important determinant of physical function [128]. Reduced strength of the quadriceps muscle as a risk factor has been found to be more common among women, especially in relation to higher body weight, and to be related to symptomatic osteoarthritis and not radiographic evidence of osteoarthritis [125; 126; 129; 130; 131]. Weakness of the hamstring muscle has not been found to increase the risk of osteoarthritis of the knee. However, individuals with osteoarthritis of the knee have well-documented hamstrings strength deficits [126; 129; 132; 133; 134].

## OTHER POTENTIAL RISK FACTORS

Several other risk factors have been identified as potential contributors to the development of osteoarthritis. Among these are malalignment, bone density, vitamin C and D deficiency, and estrogen deficiency. Additional research is needed to determine the effect of these factors on the development of disease.

### Bone Malalignment

Poor bone alignment resulting from developmental abnormalities or injury changes the load distribution on a joint [84]. The resultant increase in compressive loading in an area of the joint can increase the risk of osteoarthritis [84]. For example, genu varum (bow-leggedness) and genu valgum ("knock-kneed") have been shown to increase the risk of osteoarthritis at the medial and lateral compartment of the knee, respectively [135; 136]. However, study results have varied.

One evaluation of 110 knees with tibiofemoral osteoarthritis and 356 random control knees demonstrated that knee alignment was not associated with either radiographic tibial osteoarthritis or medial tibiofemoral osteoarthritis, and the authors suggested that malalignment was a marker of disease severity rather than a risk factor [137]. An observational, longitudinal study of the Multicenter Osteoarthritis Study cohort found that varus but not valgus alignment increased the risk of incident tibiofemoral osteoarthritis, and that both varus and valgus alignment increased the risk of disease progression in arthritic knees [138]. A third study of malalignment included 881 subjects from the Multicenter Osteoarthritis Study and 1,358 subjects from the Osteoarthritis Initiative study. The researchers found that all strata of malalignment increased the risk of progression of radiographic knee osteoarthritis and incidence as well as the risk of lateral cartilage damage [139]. Forefoot varus malalignment has been found to be related to a higher rate of hip osteoarthritis and hindfoot malalignment with a higher rate of ankle osteoarthritis [32; 140].

### Bone Density

Bone density is related to osteoarthritis, with a high bone mineral density found in association with an increased prevalence of knee, hip, and hand osteoarthritis [35; 36; 84; 141; 142; 143; 144]. Higher bone mineral density has also been reported in association with osteoarthritis of the spine [145; 146]. The reason for the relationship is not clear, and some inconsistencies and areas of controversy remain [142]. Shared genetic factors and lifetime exposure to estrogen (exogenous and endogenous) have been suggested [35; 142; 147; 148].

### Vitamin C and D Deficiency

Deficiency of vitamin C or D has been targeted as a potential contributor to osteoarthritis because of its role in antioxidation or bone metabolism, respectively [84]. The literature on the role of vitamin deficiency in osteoarthritis is limited, but the findings of some early studies have indicated that low levels of vitamin C and D may be associated with early osteoarthritic changes [35; 74]. For example, in the Framingham Osteoarthritis Study, the risk of radiographic osteoarthritis of the knee and knee pain were substantially lower among individuals in the highest tertile of vitamin C intake [149]. A study of the effect of dietary antioxidants, including vitamin C, found a significant positive association between dietary vitamin C intake and radiographic knee osteoarthritis [150]. Ascorbic acid has also been found to provide protection for human chondrocytes against oxidative stress that can lead to osteoarthritis and cartilage aging [151]. Vitamin D deficiency appears to be related to progression of osteoarthritis rather than initial development; this may be because the lack of vitamin D impairs the bone response to osteoarthritic changes [84]. Low levels of vitamin D were not related to the prevalence of osteoarthritis in the Framingham Osteoarthritis Study, but the risk for progression was three times higher for individuals in the lowest tertile of vitamin D level than for individuals in the highest tertile [152]. However, later studies found that vitamin D supplementation does not reduce knee pain or progression of osteoarthritis of the knee, though there may be an association between a low level of vitamin D and an increased risk of both new-onset hip osteoarthritis and its progression [153; 154; 155; 156; 157]. One study suggests that vitamin D deficiency exacerbates pain and dysfunction and results in a poorer quality of life in patients with knee osteoarthritis [158]. However, a subsequent study found no association between serum vitamin D concentration and knee pain in patients with osteoarthritis [159].

**Estrogen Deficiency**

There is increasing evidence that estrogens fulfill an important role in maintaining the homeostasis of articular tissues and of the joint itself and that they may also have a protective role against the development of osteoarthritis [160]. The dramatic rise in the prevalence of osteoarthritis among postmenopausal women, which is associated with the presence of estrogen receptors in joint tissues, suggests a link between osteoarthritis and loss of ovarian function [161; 162; 163; 164; 165]. Numerous clinical studies have shown that osteoarthritis is related to estrogen levels, with a greater prevalence in women than men and a clear increase in women at menopause [161; 162; 166; 167; 168]. Additional research will help shed light on the role that estrogen deficiency plays in the mechanisms of menopause-induced osteoarthritis [160].

## DIAGNOSIS

The diagnosis of osteoarthritis at most joints is made primarily on the basis of clinical findings, with imaging studies and laboratory tests more useful for ruling out other diagnoses rather than for confirming the diagnosis of osteoarthritis [40; 79; 169]. Although radiographic findings are considered to be diagnostic criteria for osteoarthritis, radiographs are not usually part of the initial diagnostic evaluation for several reasons. The primary reasons are the lack of evidence of early osteoarthritic changes on radiographs and the poor correlation between symptoms and radiographic evidence of osteoarthritis [19; 39; 40; 41]. Thus, the absence of radiographic evidence of osteoarthritis in the presence of joint-related symptoms should not exclude the diagnosis of osteoarthritis.

However, radiographs are often included in the diagnostic evaluation and are essential to the diagnosis of osteoarthritis at some joints, such as the shoulder, elbow, and ankle [30; 32; 58]. Radiographic evidence of osteoarthritis is most commonly graded according to the Kellgren-Lawrence system, which uses a scale of 0 to 4 [65]:

- 0: No radiographic evidence of osteoarthritis
- 1: Possible small osteophytes and joint space narrowing, both of which are of doubtful clinical significance
- 2: Definite osteophytes and normal joint space (or possible narrowing)
- 3: Multiple moderate osteophytes, definite narrowing of the joint space, some sclerosis, possibility of deformity of the bone contour
- 4: Large osteophytes, severe narrowing of the joint space, severe sclerosis, definite deformity of the bone contour

Similarly, no abnormal laboratory findings are associated with osteoarthritis, but again, blood tests can help rule out other diseases or conditions [9; 40]. For example, an erythrocyte sedimentation rate and/or rheumatoid factor titer can help determine a diagnosis of rheumatoid arthritis, and a complete blood count can be used to help rule out infection [30; 79].

The differential diagnosis of osteoarthritis varies according to the anatomic site as well as such patient-related factors as age, gender, and history (***Table 5***) [30; 32; 38; 40; 170; 171; 172]. In general, the differential diagnosis includes infection, traumatic injuries, bursitis, other types of arthritis, and overuse syndromes [40]. In addition, clinicians should consider secondary osteoarthritis in patients who have metabolic bone disorders, endocrine diseases, and other systemic conditions, as described earlier [40]. Ancillary testing should be done for patients who have joint pain at night, who have progressive joint pain, or who have a strong family history of inflammatory arthritis [79]. Many features on clinical evaluation and imaging studies are characteristic of osteoarthritis, and some features differ according to joint site (***Table 6***) [30; 31; 38; 58; 171].

The American College of Rheumatology (ACR) developed classification criteria for knee, hip, and hand osteoarthritis, and these have been widely accepted [171; 174; 175; 176; 177]. More recently, the European League Against Rheumatism (EULAR) has established evidence-based recommendations for diagnosis of the knee and hand [173; 178]. Evidence-based criteria for classification of osteoarthritis at other joints are not available.

Regardless of the affected joint, pain is the most common presenting feature of osteoarthritis. Because many individuals with joint pain do not seek medical care specifically for the pain, clinicians should ask their patients about joint-related symptoms at all routine office visits and other healthcare encounters [179; 180].

### HISTORY

When obtaining a history, questions should focus on the nature of joint-related symptoms, patients' self-reports of limitations in function or activities, and information related to established risk factors for osteoarthritis. The following questions can help elicit important information needed for a diagnosis:

- Do you have any joints that hurt? If so, how long have they been bothering you?
- When does the pain occur? After certain physical activities? At rest?
- Do you have relief of pain if you rest?
- Does the pain bother you at night? Does pain wake you up at night?
- Are your joints stiff when you wake up in the morning? If so, how long does the stiffness last?

| JOINT-SPECIFIC DIFFERENTIAL DIAGNOSIS FOR OSTEOARTHRITIS | |
|---|---|
| **Joint** | **Potential Diagnoses** |
| Knee | Chronic inflammatory arthritis (including rheumatoid arthritis)<br>Gout or pseudogout<br>Hip arthritis<br>Chondromalacia patellae<br>Pes anserine bursitis<br>Trochanteric bursitis<br>Patella tendonitis<br>Iliotibial band syndrome<br>Joint tumor<br>Meniscal tear<br>Anterior cruciate ligament tear |
| Hip | Trochanteric bursitis<br>Meralgia paresthetica (lateral femoral cutaneous-nerve entrapment)<br>Lumbar radiculopathy<br>Lumbar spinal stenosis<br>Chronic inflammatory arthritis (including rheumatoid arthritis and spondyloarthropathies)<br>Osteonecrosis<br>Iliopsoas tendonitis<br>Hip fracture<br>Metastatic cancer of the femur<br>Gout or pseudogout |
| Hand | De Quervain tenosynovitis<br>Carpal tunnel syndrome<br>Flexor tenosynovitis<br>Ulnar nerve compression<br>Rheumatoid arthritis (mainly targeting MCPJs, PIPJs, wrists)<br>Psoriatic arthritis<br>Carpal avascular necrosis |
| Shoulder | Rheumatoid or septic arthritis<br>Rotator cuff disease<br>Cervical disc disease<br>Frozen shoulder (soft tissue injury)<br>Cuff-tear arthropathy |
| Elbow | Infection<br>Osteochondral lesion<br>Rheumatoid or septic arthritis |
| Ankle | Gout<br>Rheumatoid or septic arthritis |
| MCPJ = metacarpophalangeal joint; PIPJ = proximal interphalangeal joint. | |
| *Source: [30; 32; 38; 40; 170; 171; 172]* | *Table 5* |

- Do the joints that hurt ever lock up or give out on you?
- Do you have a family history of osteoarthritis or rheumatoid arthritis?
- What types of recreational activities or sports do you participate in? If you play sports, do you do so for leisure or competitively?
- What is your occupation? Are there tasks or activities that are part of your job that bother any joints?
- Have you ever had an injury to a joint?
- Are there daily activities or other tasks that you cannot do because of pain or other symptoms in any joint?

| TYPICAL CHARACTERISTICS OF OSTEOARTHRITIS BY JOINT SITE | | |
|---|---|---|
| **Joint** | **Clinical Characteristics** | **Findings on Imaging Studies** |
| Knee | Pain that usually worsens with weight-bearing exercise or activity<br>Stiffness in the morning (lasting 30 minutes or less) or after periods of inactivity<br>Restricted movement<br>Crepitus<br>Osseous enlargement | Focal joint space narrowing<br>Osteophyte<br>Subchondral bone sclerosis<br>Subchondral cysts |
| Hip | Crepitus<br>Pain during internal and external rotation with the knee in full extension<br>Gait abnormality (Trendelenburg gait [waddling], abductor lurch gait, abbreviated short step, or lumbar lordotic component ["swayback"] to gait and stance) | Osteophyte<br>Joint space narrowing<br>Pseudocyst in subchondral bone<br>Increased density of subchondral bone |
| Hand | Heberden and Bouchard nodes (hard tissue enlargements on the distal interphalangeal joints)<br>Pain with use<br>Mild stiffness, either in morning or after inactivity<br>Pain affecting just one or a few joints at any one time | Osteophyte<br>Joint space narrowing<br>Subchondral bone sclerosis<br>Subchondral cyst |
| Glenohumeral Joint | Joint stiffness that worsens with activity and improves with rest<br>Crepitus<br>Decreased range of motion (external rotation and abduction)<br>Shoulder joint line tenderness<br>Joint effusion | Joint space narrowing<br>Osteophyte<br>Subchondral sclerosis<br>Cysts<br>Loss of articular cartilage |
| Elbow | Pain, stiffness, weakness<br>Loss of terminal elbow extension and impingement-type pain at terminal extension and terminal flexion (early stage)<br>Pain when carrying a heavy object at the side of the body with the elbow in extension (later stage)<br>Greater degree of motion loss and pain in the mid-arc of motion (later stage)<br>Crepitus | Preservation of articular cartilage and joint space<br>Osteophyte |
| Ankle | History of trauma/injury to the joint | Osteonecrosis<br>Bone loss<br>Subchondral cysts |
| *Source: [30; 31; 38; 58; 171; 173]* | | *Table 6* |

When considering patients' self-reports of pain and function, clinicians should understand that these self-reports can differ according to gender and race/ethnicity [48; 181; 182]. Self-reports of work or activity limitations or severe pain have been significantly more common among Black, Hispanic, and mixed-race individuals than among White individuals with osteoarthritis; the rate of self-reports for Asian/Pacific Islander and Alaska Native/American Indian populations have been similar to those for the White population [48]. Among participants in the Johnston County Osteoarthritis Project, total scores on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and scores on the pain and function subscales were significantly worse for Black individuals than for White individuals with knee osteoarthritis. The total WOMAC scores were similar for the two racial groups among individuals who had only hip osteoarthritis or hip and knee osteoarthritis [182]. The researchers hypothesized that high BMI and frequent depressive symptoms in the Black population may have contributed to the racial/ethnic differences.

Obtaining an accurate history necessitates effective patient-physician communication, which is challenging given the high number of people with inadequate language proficiency and/or health literacy [183; 184]. Clinicians should ensure that patients understand history-related questions and should seek the help of a professional translator if necessary. (A more comprehensive discussion of patient-physician communication and literacy appears later in this course.)

## PHYSICAL EXAMINATION

The physical examination should include [9; 19]:

- Assessment of body weight and BMI
- Palpation of joints for pain and/or tenderness
- Evaluation of joints for signs of swelling, enlargement, or deformity
- Determination of crepitus during joint movement
- Range of motion in the joint
- Determination of muscle strength and ligament stability

Additional evaluation may be necessary according to the joint causing symptoms.

### Osteoarthritis of the Knee

The primary symptom of osteoarthritis of the knee is pain, especially with weight-bearing exercise or activity, that improves with rest. Stiffness in the joint occurs in the morning, lasting 30 minutes or less, and may occur after periods of inactivity [185].

Individuals with osteoarthritis of the knee usually have tenderness on joint palpation, osseous enlargement, crepitus on motion, and/or limitation of joint motion [185]. Inflammation is not typically present; when present, it is mild and usually localized to the joint [185].

Radiographs of the knee are not routinely needed for a diagnosis of knee osteoarthritis. The characteristic findings of osteoarthritis on radiographs include osteophytes and joint space narrowing. Changes in the structure of the knee joint have been found more frequently on MRI than on plain radiographs, and the use of MRI in diagnosis may become more common [74]. MRI may also be helpful in ruling out other causes of knee pain with radiographic findings similar to those of osteoarthritis, such as osteochondritis dissecans and avascular necrosis [19].

The ACR developed the classification criteria for osteoarthritis of the knee with three "trees" designed to enable diagnosis based on only the clinical findings (history and physical examination), a combination of clinical and radiographic findings, or a combination of clinical and laboratory findings (***Table 7***) [174; 177]. The criteria for clinical and radiographic findings has the best reported sensitivity/specificity (91%/86%), compared with that for clinical and laboratory findings (92%/75%) and clinical findings only (95%/69%) [174].

**AMERICAN COLLEGE OF RHEUMATOLOGY CLASSIFICATION CRITERIA FOR OSTEOARTHRITIS OF THE KNEE**

| **Based on Clinical Findings Only** |
|---|
| Pain in the knee and at least three of the following:<br>• Age older than 50 years<br>• Stiffness in morning lasting less than 30 minutes<br>• Crepitus on active motion<br>• Bone tenderness<br>• Osseous enlargement<br>• No palpable warmth |
| **Based on Clinical and Radiographic Findings** |
| Pain in the knee and at least one of the following:<br>• Osteophytes (or spurs) on x-ray<br>• Age older than 50 years<br>• Stiffness in morning lasting less than 30 minutes<br>• Crepitus on active motion |
| **Based on Clinical and Laboratory Findings** |
| Pain in the knee and at least five of the following:<br>• Age older than 50 years<br>• Stiffness in morning lasting less than 30 minutes<br>• Crepitus on active motion<br>• Bone tenderness<br>• Osseous enlargement<br>• No palpable warmth<br>• Erythrocyte sedimentation rate <40 mm/hour<br>• Rheumatoid factor <1:40<br>• Signs of osteoarthritis in synovial fluid |

*Source: [175; 177]* *Table 7*

According to the EULAR guidelines on the diagnosis of knee osteoarthritis, a diagnosis can be made with 99% confidence when three symptoms and three signs are present [173]:

- Persistent knee pain
- Limited morning stiffness
- Reduced function
- Crepitus
- Restricted movement
- Osseous enlargement

### Osteoarthritis of the Hip

The clinical presentation of hip osteoarthritis is similar to that of knee osteoarthritis, with pain being the most common symptom driving individuals to seek medical care [177; 186]. Pain related to hip osteoarthritis is an ache—most often diffuse—that is usually felt during use of the joint and relieved by rest. Pain is typically gradual, variable, or intermittent; the joint may feel stiff after a period of inactivity [177; 186]. The loss of function or mobility is usually related to the degree of pain.

The strongest sign of hip osteoarthritis on physical examination is pain that is exacerbated by internal or external rotation of the hip with the knee in full extension [38; 177]. Other signs include crepitus and gait abnormalities (resulting from alterations in walking to avoid pain) [186]. Deformity and instability are late signs of severe osteoarthritis, but they are uncommon [186]. Both hips should be examined if osteoarthritis is suspected, as the disease occurs bilaterally in approximately 20% of individuals [38].

The ACR criteria for classification enable diagnosis of osteoarthritis of the hip on the basis of the clinical presentation and either laboratory or radiographic findings. According to this set of criteria, which has a reported sensitivity/specificity of 89%/91%, diagnosis requires patient-reported pain in the hip and at least two of the following three signs [175; 177]:

- Erythrocyte sedimentation rate (Westergren) of less than 20 mm/hour
- Radiographic evidence of femoral or acetabular osteophytes
- Radiographic evidence of joint space narrowing (superior, axial, and/or medial)

**Osteoarthritis of the Hand**

Osteoarthritis of the hand is characterized by pain with use, which affects one or a few joints at any one time, and mild stiffness in the morning and/or after a period of inactivity [178]. The severity of osteoarthritis-related pain varies, and the pain may be intermittent. The joints most often affected are the distal and proximal interphalangeal joints and the base of the thumb [176; 177; 178]. Individuals who have evidence of osteoarthritis at several joints in the hand are at increased risk for generalized osteoarthritis, and clinicians should evaluate such patients as appropriate [178].

Osteoarthritis of the hand may be associated with substantial limitations in function, and the clinician should ask the patient whether he or she has difficulty with such tasks as dressing, eating, writing, handling or fingering small objects, and carrying or lifting 10 pounds [44; 56]. Several validated questionnaires are available to assess function of the hand, and the choice of questionnaire depends primarily on the clinical question [171]. Individuals with symptomatic osteoarthritis of the hand also may have reduced maximal grip strength [44; 56].

The ACR criteria for classification of osteoarthritis of the hand enable diagnosis on the basis of only clinical findings [176; 177]. They consist of pain, aching, or stiffness in the hand and at least three of the following features:

- Hard tissue enlargement of at least 2 of 10 selected joints
- Hard tissue enlargement of at least two distal interphalangeal joints
- Fewer than three swollen metacarpophalangeal joints
- Deformity of at least 1 of 10 selected joints

The 10 selected joints are the second and third distal interphalangeal, the second and third proximal interphalangeal, and the first carpometacarpal joints of both hands [177]. This set of criteria yields a sensitivity/specificity of 94%/87% [176]. The evidence-based recommendations for the diagnosis of hand osteoarthritis developed by EULAR support the ACR's criteria of only clinical findings, stating that a confident clinical diagnosis can be made in adults older than 40 years of age on the basis of the described clinical findings [171].

Hard tissue enlargements on the distal interphalangeal joints (Heberden and Bouchard nodes) are the clinical finding that is most characteristic of osteoarthritis of the hand [56; 176; 177]. Although radiographic findings are not an established diagnostic criterion, evidence of osteophytes is the only unique radiographic criterion for a diagnosis [176]. Other classic radiographic findings include joint space narrowing, subchondral bone sclerosis, or subchondral cysts [171; 176]. The diagnosis of hand osteoarthritis does not require blood tests, but such tests may be helpful in excluding coexisting disease or in identifying an inflammatory arthritis [171].

**Osteoarthritis of the Shoulder**

Pain related to osteoarthritis of the shoulder is typically progressive, related to activity, deep in the joint, and often localized posteriorly [30]. Pain is usually present at rest and interferes with sleep, with nocturnal pain becoming more common as the disease progresses. More advanced disease is also associated with stiffness that limits function.

Younger patients with shoulder pain should be asked about previous trauma, dislocation, or surgery for shoulder instability, as all have been related to the development of osteoarthritis [30]. In the early stages of disease, the findings of the physical examination may be unremarkable. Some signs indicative of osteoarthritis are painful crepitus, enlargement of the joint, tenderness at the joint line, and joint effusion. The range of motion is usually decreased, especially in external rotation and abduction. In advanced stages of disease, grinding may be audible or palpable when mechanical stress is placed on the shoulder. Signs that are not indicative of shoulder osteoarthritis are lack of pain on palpation or passive range of motion (e.g., bursitis, rotator cuff disease, or biceps tenderness) and loss of passive or active range of motion (e.g., calcific tendinitis or idiopathic adhesive capsulitis) [187].

Unlike the case with osteoarthritis at other sites, imaging studies are essential for the diagnosis of osteoarthritis of the shoulder [30]. Signs of early disease include slight narrowing of the joint space, small osteophytes, subchondral sclerosis, cysts, and eburnation or advanced loss of articular cartilage. Narrowing of the joint space can be best detected with either an axillary view or an anteroposterior view, with the arm held in 45 degrees of abduction [188]. MRI can demonstrate wearing of articular cartilage, and computed tomography arthrograms can be used to localize articular defects [30].

A blood panel can help identify infection. An erythrocyte sedimentation rate greater than 45 mm/hour may indicate rheumatoid arthritis, an underlying malignancy, or chronic infection. These blood tests are sensitive but not specific in determining causes of shoulder pain [189].

**Osteoarthritis of the Elbow**

Individuals with osteoarthritis of the elbow typically have pain, stiffness, and weakness in the joint [31]. Later stage disease is associated with pain when carrying a heavy object at the side of the body with the elbow in extension. The history is important when evaluating symptoms related to the elbow because of the strong relationship between trauma or occupation with osteoarthritis, especially in individuals who are younger than 40 years of age [58]. Primary osteoarthritis of the elbow is often associated with osteoarthritis at another joint site, especially the second and third metacarpophalangeal joints, the knee, and the hip, and those joints should be evaluated as appropriate [190].

Range of motion should be examined in flexion-extension and pronation-supination. Most patients will have pain at the endpoints of range of motion rather than at other points throughout the arc of motion. Crepitus can usually be heard during range of motion.

As with osteoarthritis of the shoulder, osteoarthritis of the elbow can be diagnosed with standard radiographs, and anteroposterior and lateral projections are best [31; 58]. A distinction of primary elbow osteoarthritis is preservation of the joint space, even when disease is at an advanced stage [31; 58]. Other radiographic characteristics of primary osteoarthritis are an anterior and medial osteophyte (involving the coronoid process) and a posteromedial osteophyte (olecranon process). The location and size of osteophytes can be determined by computed tomography (CT) with three-dimensional reconstructions [58]. It may be difficult to detect loose bodies on plain radiographs [58].

**Osteoarthritis of the Ankle**

A history of ankle fracture or ligamentous injury is a hallmark feature of osteoarthritis of the ankle [32]. Diagnostic evaluation includes radiographs of the ankles made with the patient standing. MRI is also recommended, as it can provide evidence of osteonecrosis as well as indicate the amount of involvement, the extent of bone loss, and the size of subchondral cysts [32].

## TREATMENT OPTIONS

There is currently no curative therapy for osteoarthritis, and treatments to alter or arrest the disease process are few and mostly ineffective [19]. However, researchers are actively attempting to improve these medications to make them more effective, and, as of 2019, several novel drugs for blocking inflammation using antibiodies and pathway inhibitors are in various phases of clinical trials [191; 192]. Current management is focused on decreasing pain and increasing function [193; 194]. Several treatment approaches have been used for osteoarthritis and subsequently included in practice guidelines. The range in options has made it difficult for clinicians to determine which ones are most effective; more than 50 treatment modalities have been addressed in 23 guidelines for the management of knee and hip osteoarthritis alone [193]. These guidelines have been established by professional organizations in the United States, such as the ACR, the American Academy of Orthopaedic Surgeons (AAOS), and the American Geriatrics Society (AGS); and in Europe, such as EULAR, the Osteoarthritis Research Society International (OARSI), and the National Institute for Health and Clinical Excellence (NICE). The guidelines have addressed osteoarthritis in general, osteoarthritis at specific joints (primarily the knee and hip), and exercise programs (***Table 8***) [171; 185; 193; 194; 195; 196; 197; 198; 199]. In addition, the Agency for Healthcare Research and Quality (AHRQ) has commissioned research for comparative effectiveness studies and evidence reports related to osteoarthritis [200; 201; 202].

Despite the availability of these guidelines, gaps in evidence-based recommendations exist. There are currently no evidence-based guidelines on the management of osteoarthritis of the elbow, ankle, or spine; there is only one (European) guideline on management of osteoarthritis of the hand [171]. Most of the treatment options in use are not based on clinical studies of these specific areas but are instead extracted from evidence obtained from clinical studies of other limb joints [203]. Adding to the challenge of selecting appropriate therapy is evolving evidence on the efficacy of specific options; systematic reviews, meta-analyses, and randomized controlled clinical trials have demonstrated that many commonly used treatment options for osteoarthritis offer no or limited benefit.

**CLINICAL PRACTICE GUIDELINES FOR THE DIAGNOSIS AND MANAGEMENT OF OSTEOARTHRITIS**

**Knee**

American Academy of Orthopaedic Surgeons. Management of Osteoarthritis of the Knee (Non-Arthroplasty). Available at https://www.aaos.org/globalassets/quality-and-practice-resources/osteoarthritis-of-the-knee/oak3cpg.pdf.

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Fernandes L, Hagen KB, Bijlsma JW, et al. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. *Ann Rheum Dis*. 2013;72(7):1125-1135.

Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Rheumatol*. 2020;72(2):220-233.

Jordan K, Arden NK, Doherty M, et al. EULAR recommendations 2003: an evidence based approach to the management of knee osteoarthritis: report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Ann Rheum Dis*. 2003;62(12):1145-1155.

Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage*. 2008;16(2):137-162.

Zhang W, Nuki G, Moskowitz RW, et al. OARSI recommendations for the management of hip and knee osteoarthritis: part III: changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthritis Cartilage*. 2010;18(4):476-499.

Zhang W, Doherty M, Peat G, et al. EULAR evidence-based recommendations for the diagnosis of knee osteoarthritis. *Ann Rheum Dis*. 2010;69(3):483-489.

VA/DoD Clinical Practice Guideline for the Non-Surgical Management of Hip and Knee Osteoarthritis. Version 2.0 – 2020. Available at https://www.healthquality.va.gov/guidelines/CD/OA/VADoDOACPG.pdf.

McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage*. 2014;22(3):363-388.

**Hip**

Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Rheumatol*. 2020;72(2):220-233.

Fernandes L, Hagen KB, Bijlsma JW, et al. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. *Ann Rheum Dis*. 2013;72(7):1125-1135.

Zhang W, Doherty M, Arden N, et al. EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis*. 2005;64(5):669-681.

Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage*. 2008;16(2):137-162.

Zhang W, Nuki G, Moskowitz RW, et al. OARSI recommendations for the management of hip and knee osteoarthritis: part III: changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthritis Cartilage*. 2010;18(4):476-499.

**Hand**

Zhang W, Doherty M, Leeb BF, et al. EULAR evidence based recommendations for the management of hand osteoarthritis: report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis*. 2007;66(3):377-388.

Zhang W, Doherty M, Leeb BF, et al. EULAR evidence-based recommendations for the diagnosis of hand osteoarthritis: report of a task force of EXCISIT. *Ann Rheum Dis*. 2009;68(1):8-17.

**Shoulder**

Izquierdo R, Voloshin I, Edwards S, et al. Treatment of glenohumeral osteoarthritis. *J Am Acad Orthop Surg*. 2010;18(6):375-382.

*Table 8 continues on the next page.*

| CLINICAL PRACTICE GUIDELINES FOR THE DIAGNOSIS AND MANAGEMENT OF OSTEOARTHRITIS *(Continued)* |
|---|
| **Other** |
| National Clinical Guideline Centre. *Osteoarthritis: Care and Management in Adults* London: National Institute for Health and Care Excellence; 2014. |
| American Geriatrics Society Panel on Exercise and Osteoarthritis. Exercise prescription for older adults with osteoarthritis pain: consensus practice recommendations. *J Am Geriatr Soc.* 2001;49(6):808-823. (Supplement to practice recommendations available at http://agingblueprint.org/wers/2014/12/oae_guidelines.pdf.) |
| Roddy E, Zhang W, Doherty M, et al. Evidence-based recommendations for the role of exercise in the management of osteoarthritis of the hip or knee—the MOVE consensus. *Rheumatology.* 2005;44(1):67-73. |
| Brosseau L, Wells GA, Tugwell P, et al. Ottawa Panel evidence-based clinical practice guidelines for the management of osteoarthritis in adults who are obese or overweight. *Phys Ther.* 2011;91(6):843-861. |
| *Source: Compiled by Author* *Table 8* |

As clinicians on the frontline of care, primary care providers and nurses are typically the first to see individuals with symptoms indicative of osteoarthritis. Primary care providers can coordinate the management of osteoarthritis, and a multidisciplinary approach is best. The ACR and the Association of Rheumatology Health Professionals (a division of the ACR) support such an approach, noting that the healthcare team may include a rheumatologist, primary physician, nurse, nurse practitioner, physician assistant, physical therapist, occupational therapist, physiatrist, psychiatrist, psychologist, orthopedic surgeon, social worker, registered dietician, vocational counselor, and others [204]. A primary care physician should consider referral to a rheumatologist in the following situations [19]:

- Atypical signs and symptoms (e.g., pain at night, prolonged stiffness in the morning, involvement of multiple joints)
- Overall evaluation to address needs for nonpharmacologic treatment
- Lack of response to standard treatment
- Need for operative procedures (arthroscopy and arthroplasty)

The optimal management of osteoarthritis encompasses both nonpharmacologic and pharmacologic measures, beginning with basic modalities and following a so-called pyramid approach as the disease progresses or symptoms do not respond [205]. Several factors should be considered when selecting treatment modalities, including risk factors (e.g., age, comorbidity, overweight/obesity), the level of pain and functional limitations, signs of inflammation, and degree of structural damage [206].

Many treatment options are associated with benefits and risks, and the clinician should discuss the benefits and risks with patients and support their participation in the decision-making process [207; 208]. Patient preferences are an important consideration when choosing treatment options and establishing treatment goals, and the ACR advocates care that addresses treatment goals that are meaningful to the individual patient [204]. Decision aids can help enhance patients' knowledge of treatment options, improve patients' participation in their care, and produce realistic expectations of outcomes [208]. Decision aids for osteoarthritis have been developed in a variety of media (e.g., print, online, video) and are available online (https://decisionaid.ohri.ca) [208].

The pain and disability associated with osteoarthritis often has a substantial psychologic and social effect. It is important to discuss these aspects with patients and to address psychologic issues, especially depression, in order for treatment measures to be effective [88].

## NONPHARMACOLOGIC APPROACHES

Several nonpharmacologic treatment options have been found to be effective in managing osteoarthritis (***Table* 9**).

### Education and Self-Management

Education and self-management, through lifestyle modifications are universally recognized as the core of treatment in clinical guidelines [193]. This recommendation is based on research showing that education helps patients become more involved in their care, leading to improved outcomes [207]. The AHRQ notes that an effective partnership is the key to the effective management of osteoarthritis; the healthcare professional's role in this partnership is to [207]:

- Encourage patients to change their behavior to improve symptoms or slow disease progression
- Promote the proper use of medications
- Instruct patients on how to interpret and report symptoms accurately
- Support patients' efforts to maintain normal activities
- Help patients adjust to new social and economic circumstances and cope with emotional consequences

  

| EVIDENCE-BASED NONPHARMACOLOGIC OPTIONS FOR THE MANAGEMENT OF OSTEOARTHRITIS | |
|---|---|
| **Intervention** | **Joint** |
| Patient education and self-management | All joints |
| Weight loss/maintenance of optimum weight | Knee, hip |
| Regular exercise | Knee, hip |
| Physical therapy strategies<br>Range-of-motion exercises<br>Strengthening exercises<br>Application of heat or therapeutic ultrasound | Knee, hip, hand, elbow |
| Braces, orthotics, walking aids | Knee, hip, ankle, hand |
| *Source: [185; 193]* | *Table 9* |

Clinicians should emphasize to patients that adhering to the management program will alleviate their symptoms, improve their function, and enhance their quality of life. Education should be tailored to address individual needs. For example, patients who participate in sports should be advised to avoid sports with direct contact and high impact and to wear protective equipment to prevent injury [84]. Similarly, for patients in occupations with high risk for osteoarthritis, clinicians should discuss the importance of avoiding high-risk tasks. Education and training in ergonomic principles, pacing of activity, and use of assistive devices should be offered to patients with hand osteoarthritis [171]. It is also essential to encourage patients with osteoarthritis of the glenohumeral joint or the elbow to modify activities that led to the development of the disease [31; 58]. Periodic contact during follow-up can help promote self-management [193].

Clinicians should also encourage patients to participate in formal self-management programs in the community or online and to use reliable educational resources, such as the Arthritis Foundation (https://www.arthritis.org) [172].

EVIDENCE-BASED PRACTICE RECOMMENDATION

Self-management programs are recommended by the American Academy of Orthopaedic Surgeons to improve pain and function for patients with knee osteoarthritis.

(https://www.aaos.org/globalassets/quality-and-practice-resources/osteoarthritis-of-the-knee/oak3cpg.pdf. Last accessed September 22, 2022.)

**Strength of Recommendation:** Strong (Evidence from two or more high-quality studies with consistent findings for recommending for or against the intervention)

When educating a patient about osteoarthritis and its management, it is essential to ensure that he or she understands the treatment plan and his or her role in self-management. However, according to the National Assessment of Health Literacy, 14% of individuals in the United States have "below basic" health literacy, which means they lack the ability to understand health information and make informed health decisions [183; 209]. Data from 2017 indicate that this figure is 19% [210]. Understanding the problem of health literacy is especially important for clinicians managing osteoarthritis, as low health literacy is more common among older individuals, the population most affected by the disease [211]. Health literacy also varies widely according to race/ethnicity, and level of education, and clinicians are often unaware of the literacy level of their patients [210; 211; 212]. Predictors of limited health literacy are poor self-rated reading ability, low level of education, male gender, and non-White race [212; 213]. Ensuring that patients understand health information is essential, as limited health literacy has been associated with poor health outcomes [214].

Several instruments are available to test patients' literacy level, and they vary in the amount of time needed to administer and reliability in identifying low literacy. A review of several instruments demonstrated that the two most accurate tools for identifying literacy are the Rapid Estimate of Adult Literacy in Medicine (REALM) and the shortened version of the Test of Functional Health Literacy in Adults (S-TOFHLA) [211]. REALM takes 3 minutes to administer, whereas S-TOFHLA takes 7 to 12 minutes to administer [211]. More rapid testing is available in the form of the Newest Vital Sign (NVS), an instrument named to promote the assessment of health literacy as part of the overall routine patient evaluation [183; 215]. The NVS takes fewer than three minutes to administer, has correlated well with more extensive literacy tests, and has performed moderately well at identifying limited literacy [211; 212]. Two questions have also been found to perform moder-

ately well in identifying patients with inadequate or marginal literacy: "How confident are you in filling out medical forms by yourself?" and "How often do you have someone help you read health information?" [211].

Compounding health literacy are language and cultural barriers, which have the potential for far-reaching effect, given the growing percentages of racial/ethnic populations. According to the U.S. Census Bureau, more than 66 million Americans speak a language other than English in the home, with approximately 25.3 million of them (8.2% of the population) speaking English less than "very well" [216]. It has been suggested that when patients are first evaluated, they should be asked what language is spoken at home and if they speak English "very well" [217]. In addition, patients should also be asked what language they prefer for their medical care information, as some patients prefer their native language even though they have said they can understand and discuss symptoms in English [217]. Many studies have demonstrated that the lack of an interpreter for patients with limited English proficiency compromises the quality of care and that the use of professional interpreters improves communication (errors and comprehension), utilization, clinical outcomes, and patient satisfaction with care.

"Ad hoc" interpreters (e.g., family members, friends, and bilingual staff members) are often used instead of professional interpreters for a variety of reasons, including convenience and cost. However, clinicians should check with their state's health officials about the use of ad hoc interpreters, as several states have laws about who can interpret medical information for a patient [218]. Even when allowed by law, the use of a patient's family member or friend as an interpreter should be avoided, as the patient may not be as forthcoming with information and the family member or friend may not remain objective [218]. Children should especially be avoided as interpreters, as their understanding of medical language is limited and they may filter information to protect their parents or other adult family members [218]. Individuals with limited English language skills have actually indicated a preference for professional interpreters rather than family members [219].

Most important, perhaps, is the fact that clinical consequences are more likely with ad hoc interpreters than with professional interpreters [220]. A systematic review of the literature showed that the use of professional interpreters facilitates a broader understanding and leads to better clinical care than the use of ad hoc interpreters, and many studies have demonstrated that the lack of an interpreter for patients with limited English proficiency compromises the quality of care and that the use of professional interpreters improves communication (errors and comprehension), utilization, clinical outcomes, and patient satisfaction with care [221; 222].

Clinicians should adapt their discussions and educational resources to a patient's identified health literacy level and degree of language proficiency. The use of plain language (free of medical jargon), asking patients to repeat pertinent information, regularly assessing recall and comprehension, and using translated educational materials can all help ensure that patients better understand their disease and its management, ultimately leading to higher quality care.

### Weight Reduction

Given the strong correlation between overweight/obesity (defined as a BMI greater than 25) and osteoarthritis of the knee and hip, weight reduction and maintenance of a healthy weight are central to guidelines on the management of osteoarthritis at these sites [185; 198; 206; 223; 224]. A systematic review showed that a moderate weight-loss program (0.25% of body weight per week) can reduce pain and physical disability for individuals with osteoarthritis of the knee [225]. In its 2021 guideline for the treatment of osteoarthritis of the knee, the AAOS recommends weight reduction, specifically, achieving and/or maintaining a BMI ≤25 [198].

The recommended approach to weight loss is through dietary modifications and an exercise program [224]. The Arthritis, Diet, and Activity Promotion Trial (ADAPT), which involved 316 overweight or obese adults with knee osteoarthritis, demonstrated that an 18-month program of modest weight loss and modest exercise provided the most benefit (compared with a diet-only or exercise-only program) [226]. Individuals in the diet-plus-exercise group had significant improvements in self-reported physical function, six-minute walk distance, stair-climb time, and knee pain. The 2019 ACR guideline specifies weight reduction counseling [185].

### Exercise and Physical Therapy

Regular, moderate exercise can help maintain overall health, muscle strength, and range of motion of the joint. In addition, several physical therapy strategies can help improve function and relieve pain.

#### *Regular Exercise*

Some patients may fear that regular exercise will exacerbate pain, but a review of the literature has shown that moderate exercise does not increase the risk for progression of osteoarthritis, provided that care is taken to avoid injury [110; 227]. The goal of an exercise program is to control pain, increase flexibility, and improve muscle strength and endurance [228]. The exercise program should be individualized to the patient, with consideration given to the patient's age, comorbidities, and mobility [229]. Guidelines suggest that exercise should be prescribed for all patients with osteoarthritis, regardless of age, severity of pain and disability, and comorbidity [199]. The American Geriatric Society notes that absolute contraindications to an exercise program include uncontrolled arrhythmias, third-degree heart block, changes on recent

  

electrocardiography, unstable angina, acute myocardial infarction, and acute congestive heart failure [228]. Relative contraindications include cardiomyopathy, valvular heart disease, poorly controlled blood pressure, and uncontrolled metabolic disease [228].

Promoting exercise as part of an overall positive lifestyle change can increase the effectiveness of the program [229]. Supervised group exercise and home-based programs have been shown to be equally effective, allowing patients to select the type of program they prefer [229]. The Ottawa Panel recommends that significant weight-loss occur before starting weight-bearing exercise (particularly for obese patients) in order to maintain joint integrity and to avoid joint disease and dysfunction [224].

Low-impact aerobic exercise, such as walking, bicycling, swimming, or water aerobics, has shown to offer substantial benefit in terms of improved physical function, reduction of pain and disability, and enhanced perceived quality of life in individuals with knee osteoarthritis, especially overweight/obese individuals [198; 227; 230; 231]. Although there is little evidence that exercise is of benefit to individuals with hip osteoarthritis, one systematic review found that land-based (as opposed to water-based) therapeutic exercise programs can reduce pain and improve physical function [229; 231]. Adherence is the primary predictor of long-term outcome from exercise for the management of knee or hip osteoarthritis; because of this, clinicians should encourage patients to engage in exercises they enjoy, as this can enhance the likelihood of long-term adherence. Long-term monitoring, frequent contact during follow-up, and/or involving family members in the program may also enhance adherence [193; 229; 232].

In 2000, the ACR guidelines for the management of knee and hip osteoarthritis included a recommendation for aerobic exercise [71]. A year later, the AGS published evidence-based recommendations for exercise as part of managing osteoarthritis in older individuals. (These recommendations were not joint-specific.) In 2005, a European multidisciplinary expert panel developed evidence-based recommendations for exercise to manage osteoarthritis of the knee or hip [229]. The AAOS incorporated these previous recommendations into its 2008 guideline for the treatment of knee osteoarthritis, noting that patients should be encouraged to participate in low-impact aerobic fitness exercises (level of evidence: I, A) and quadriceps strengthening (level of evidence: II, B) [232]. Subsequent reviews of the literature have supported that exercise reduces pain and improves physical function [227; 233]. The 2021 AAOS guideline on the treatment of knee osteoarthritis strongly recommends the implementation of a variety of physical therapy and exercise modalities, including low-impact aerobic exercise, aquatic exercise, strength training, self-management programs, and neuromuscular education [198]. Exercise recommendations should be consistent with national guidelines. The 2019 ACR Technical Expert Panel recommends land- or water-based aerobic exercise for all patients (depending on patient preference) except those who are extremely overweight or aerobically deconditioned; for these patients, water-based exercise is recommended until conditioning (i.e., improved aerobic capacity) is achieved [185].

### *Physical Therapy Strategies*

Substantial improvement in symptoms related to osteoarthritis of the knee has been achieved through several physical therapy strategies, including range-of-motion (flexibility) exercises, muscle stretching, and soft tissue mobilization [172]. A combination of physical therapy (to the knee as well as to the lumbar spine, hip, and ankle, as required) and a standardized exercise program provided more benefit than placebo (subtherapeutic ultrasound to the knee) in a small randomized study (83 patients) of the management of knee osteoarthritis [234]. Patients treated with the combination therapy had clinically and statistically significant improvements in WOMAC score and six-minute walk distance, whereas no improvements were found in the placebo group. The benefits were sustained at one year, and fewer patients in the treatment group had undergone knee arthroplasty (5% vs. 20%) at that time. Another small randomized study compared home-based physical therapy with clinically based physical therapy [235]. The 134 participants with knee osteoarthritis were randomly assigned to a clinic treatment group or a home exercise group. The clinic treatment group received supervised exercise and individualized manual therapy; they also completed a four-week home exercise program. The home exercise group completed the four-week home exercise program, with reinforcement at a clinic visit two weeks later. Both groups showed clinically and statistically significant improvements in six-minute walk distances and WOMAC scores at four weeks and eight weeks. By four weeks, WOMAC scores had improved by 52% in the clinic treatment group and by 26% in the home exercise group. Average six-minute walk distances had improved about 10% in both groups. At one year, both groups were substantially and about equally improved over baseline measurements. Subjects in the clinic treatment group were less likely to be taking medications for their arthritis and were more satisfied with the overall outcome of their rehabilitative treatment compared with subjects in the home exercise group [235].

The AGS guidelines recommend flexibility exercises, strengthening exercises, and endurance exercises, along with heat modalities, for older patients with all types of osteoarthritis. Range-of-motion (flexibility) exercises can help decrease stiffness, increase joint mobility, and prevent soft-tissue contractures [228]. Static stretching can improve range of motion. Exercises that combine flexibility and resistance training (e.g., yoga, tai chi) have significant therapeutic benefit for knee osteoarthritis [185; 198]. The goal of strengthening exercises is to increase the strength of the muscles that support the affected joint [228]. Exercises to strengthen the quadriceps muscles have led to improvements in pain and function for individuals with knee osteoarthritis [172]. In addition, studies suggest

that strengthening the quadriceps muscles may help delay progression of knee and hip osteoarthritis [229]. In general, patients should begin a strengthening exercise regimen with isometric exercises and advance to isotonic resistance exercises as tolerated [228]. Isometric, isotonic, and isokinetic training have similar long-term benefits [198]. In general, it appears that exercise is beneficial, but the mode of exercise may not matter as much as engaging in any exercise program [198].

The findings of a systematic review suggest that therapeutic ultrasound may help reduce pain and increase function for patients with osteoarthritis of the knee [236]. However, the quality of the evidence is low, which left the authors of this and another review uncertain about the magnitude of the effects of the treatment modality [236; 237]. The AAOS guideline on the treatment of knee osteoarthritis refrains from making a recommendation for or against therapeutic ultrasound; however, the authors of the guideline reviewed several studies showing evidence of its benefit, particularly when combined with various forms of exercise [198].

With regard to other joints, EULAR guidelines recommend an exercise regimen that involves range-of-motion and strengthening exercises for all individuals with osteoarthritis of the hand [178]. The guidelines also recommend local application of heat, especially before exercise; heat can be applied with a hot pack or paraffin wax [178]. Thermal agents/modalities in combination with exercise are also endorsed by the ACR [185].

The AAOS found inconclusive evidence for physical therapy as an effective treatment option for osteoarthritis of the glenohumeral joint and is unable to recommend for or against physical therapy as part of initial treatment of the condition [197]. Similarly, a supervised physical therapy program is not routinely a treatment approach for osteoarthritis of the ankle [32]. Physical therapy should begin in the early stages of osteoarthritis of the elbow (mild pain and loss of less than 15 degrees of motion) [31]. Strategies may include gentle range-of-motion exercises to maintain mobility and strength [31].

### Braces, Orthotics, Walking Aids, and Footwear

#### *Braces*

Although valgus or varus bracing can theoretically relieve pain and improve function by shifting joint load away from the medial or lateral compartment of the knee, respectively, the AAOS found inconclusive evidence of the efficacy of these types of braces in terms of relieving pain or improving function or quality of life [198]. Braces can provide significant pain relief and improved function to patients who have unicompartmental knee osteoarthritis. Braces also can provide a subjective feeling of more normal tibiofemoral kinematics. There is a theoretical benefit of increased confidence in the knee during activities by providing a sense of security to the knee. Apart from some skin irritation or discomfort, there are almost no harms in trialing a brace [198].

With regard to other joints, a thumb splint may be helpful for people with osteoarthritis of the thumb base, and a brace has been suggested as part of conservative management of osteoarthritis of the ankle. However, these recommendations are based on expert opinion only [32; 178].

#### *Orthotics*

It has been proposed that lateral and medial wedges may help relieve the symptoms of medial and lateral compartment osteoarthritis of the knee, respectively, by reducing joint load. However, studies have not provided evidence that wedges alone improve osteoarthritis-related symptoms [172; 198; 238]. The ACR guidelines suggest that patients may benefit from the use of wedged insoles to correct abnormal biomechanics related to varus deformity of the knee, but the AAOS recommends that lateral heel wedges not be prescribed for patients with symptomatic medial compartmental osteoarthritis of the knee [185; 198].

#### *Walking Aids*

The ACR recommends use of a cane on the contralateral side to help decrease pain and improve function for patients who have persistent pain related to knee or hip osteoarthritis [172; 185].

#### *Footwear*

Clinicians should also advise patients with hip or knee osteoarthritis about appropriate footwear; the optimum shoe may be one that is flat or has a low heel and that is flexible (rather than stabilizing) [238]. Foot orthoses to correct varus malalignment of the forefoot may help reduce pain in the hip among individuals with osteoarthritis of that joint [140]. Modifications to footwear may be helpful for people with osteoarthritis of the ankle [32].

#### *Other*

The ACR recommends patellar taping for the short-term relief of pain and improvement of function among individuals with symptomatic osteoarthritis of the knee [185]. Although the AAOS has previously endorsed taping, the 2021 update does not address this approach [198; 232].

### Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation (TENS) has been used as part of management of knee osteoarthritis, but the data on its effectiveness are conflicting. One review of the literature (systematic reviews published between 2000 and 2007) demonstrated evidence of moderate quality that TENS reduces pain [233]. The authors of a subsequent review (up to 2008) reported that they could not confirm the benefit of TENS for the relief of pain, noting that the review was inconclusive because of the inclusion of small trials of questionable quality [239]. The ACR recommends the use of electrical stimulation only for patients with severe pain who are candidates for total

  

| EVIDENCE-BASED PHARMACOLOGIC OPTIONS FOR THE MANAGEMENT OF OSTEOARTHRITIS[a] | |
|---|---|
| **Pharmacologic Approach** | **Notes** |
| Oral analgesics | Insufficient evidence to recommend for osteoarthritis of the shoulder |
| Acetaminophen | Up to 4 g/day |
| Nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., naproxen, ibuprofen) | A gastroprotective agent (proton-pump inhibitor) should be prescribed for patients at high risk for gastrointestinal complications |
| Cyclooxygenase-2 (COX-2) selective NSAIDs | Some agents associated with an increased risk of myocardial infarction |
| Tramadol | Considered separately from opioid analgesics due to modulatory effect on serotonin and norepinephrine levels |
| Opioid analgesics | No recommendation for or against use for osteoarthritis of the hip, knee, or shoulder. Should not be used for osteoarthritis of the hand. Weak opioids may be used for pain refractory to other pharmacologic agents. |
| Topical analgesics (e.g., NSAIDs, capsaicin) | Insufficient evidence to recommend for osteoarthritis of the shoulder |
| Intra-articular corticosteroids | Insufficient evidence to recommend for osteoarthritis of the shoulder<br>Provide short-term relief (up to four weeks) for all joints |
| Viscosupplementation (hyaluronan) | Conditionally recommended for certain patients<br>Recommended only for osteoarthritis of the knee or shoulder<br>Schedule of weekly injections has varied from three to five consecutive weeks |
| [a]No evidence-based guidelines are available for osteoarthritis of the elbow or ankle. | |
| *Source: [185; 193; 197; 198; 232]* | *Table 10* |

knee arthroplasty but who are unwilling or unable to undergo the procedure (i.e., contraindication due to comorbidities/medication) [185]. The AAOS is unable to recommend for or against any form of electrotherapy [198].

**Acupuncture**

The available literature demonstrates that acupuncture provides minimal, short-term relief of pain related to knee osteoarthritis [233; 240; 241]. Acupuncture was considered to be a therapy "under investigation" at the time of publication of the 2000 ACR guidelines for the management of osteoarthritis of the knee and hip [71]. The 2019 ACR expert panel recommends the use of acupuncture only for patients with severe pain who are candidates for total knee arthroplasty but who are unwilling or unable to undergo the procedure [185]. The AAOS applied a limited strength recommendation for the use of acupuncture as an adjunctive therapy for pain relief in patients with symptomatic osteoarthritis of the knee. This is a downgraded recommendation because of inconsistent evidence and a lack of internal consistency with recommendations of equal supporting evidence [198]. No recommendations have been made regarding the use of acupuncture as part of the treatment of osteoarthritis at other joint sites.


According to the American Academy of Orthopaedic Surgeons, acupuncture may improve pain and function in patients with knee osteoarthritis.

(https://www.aaos.org/globalassets/quality-and-practice-resources/osteoarthritis-of-the-knee/oak3cpg.pdf. Last accessed September 22, 2022.)

**Strength of Recommendation**: Limited (Evidence from two or more moderate-quality studies with consistent findings, or evidence from a single high-quality study for recommending for or against the intervention)

## PHARMACOLOGIC THERAPIES

No drugs have been found to effectively alter the disease process or the structural properties of the joint; therefore, the goal of pharmacologic therapies is to relieve pain. Oral analgesics form the basis of pharmacologic management, and other effective pharmacologic options, depending on the joint, include topical analgesics, viscosupplementation, and intra-articular corticosteroids (***Table 10***).

Educating patients about their pharmacologic treatment plan is crucial. A questionnaire designed to assess patients' knowledge of osteoarthritis and its management demonstrated a substantial lack of knowledge about analgesics [242]. Fewer than one-third of the patients knew that they could take analgesics prophylactically, and 70% did not know that analgesics should be taken when pain starts to build. In addition, approximately one-third did not know that nonsteroidal anti-inflammatory drugs (NSAIDs) should be taken with food or following a meal [242]. Another small study showed that patients with multiple coexisting conditions are dissatisfied with the complex medication regimen required for comorbidities [243]. Patients in this study were unclear on how to take analgesics on an "as needed" basis, pointing to the need for clearer guidance from clinicians and other healthcare professionals [243].

### Oral Analgesics

Because of the wide range of pain relievers available, the challenge is to select an agent that will provide optimum relief with minimum adverse events. The oral pain relievers used for osteoarthritis include acetaminophen, nonselective NSAIDs, cyclooxygenase-2 (COX-2) selective NSAIDs, opioids, and tramadol. The 2021 AAOS guideline specifies NSAIDs (oral or topical) as first-line pharmacologic treatments for symptomatic osteoarthritis of the knee. The guideline does not recommend tramadol, citing a significant increase of adverse events and lack of efficacy at improving pain or function for treatment of osteoarthritis of the knee [198]. The 2019 ACR guideline recommends NSAIDs (including COX-2-selective agents) and tramadol as first-line treatment for hand osteoarthritis, and acetaminophen, NSAIDs, and tramadol for knee and hip osteoarthritis [185].

Some guidelines recommended acetaminophen as the initial analgesic for the management of mild-to-moderate pain related to osteoarthritis, but this recommendation has since been shown to be questionable [193]. A comparative effectiveness study conducted by the AHRQ found good evidence that acetaminophen is modestly inferior in efficacy compared with NSAIDs but has a lower risk of gastrointestinal complications [244]. An update to this study found that no currently available analgesic offered a clear overall advantage compared with the others [200]. Its original findings on acetaminophen remained the same, with the addition that acetaminophen poses a higher risk of liver injury [200]. Other research has shown that NSAIDs are more effective than acetaminophen for relieving osteoarthritis-related pain, especially moderate-to-severe pain [245]. The 2021 AAOS guideline provides a strong recommendation for oral acetaminophen to improve pain and function in the treatment of knee osteoarthritis when not contraindicated [198]. The working group noted that when oral acetaminophen was compared to NSAIDs, the use of oral NSAIDs provided a significant reduction in pain and improved function. As a result, providers may consider using oral NSAIDs instead of acetaminophen when a contraindication to oral NSAIDs does not exist [198]. NSAIDs should be prescribed at the lowest effective dose, and their long-term use should be avoided [193]. A COX-2 selective agent or an NSAID with a prescription for a gastroprotective agent (such as a proton-pump inhibitor) may be used for patients who have an increased risk for gastrointestinal complications [193].


The American Academy of Orthopaedic Surgeons asserts that oral NSAIDs and/or acetaminophen are recommended to improve pain and function in the treatment of knee osteoarthritis, when not contraindicated.

(https://www.aaos.org/globalassets/quality-and-practice-resources/osteoarthritis-of-the-knee/oak3cpg.pdf. Last accessed September 22, 2022.)

**Strength of Recommendation**: Strong (Evidence from two or more high-quality studies with consistent findings for recommending for or against the intervention)

There is good evidence that nonselective NSAIDs and COX-2-selective NSAIDs have comparable efficacy and that COX-2-selective agents are comparable to each other [200; 246]. Although COX-2-selective agents have better tolerability in general compared with NSAIDs, there is considerable variability across individual drugs in terms of protection against serious gastrointestinal events [246]. In addition, some COX-2 selective NSAIDs have been associated with an increased risk of myocardial infarction, and these drugs should be used with caution in patients with cardiovascular risk factors [200; 246].

Studies have found that opioids were more effective overall than control interventions with respect to pain relief and improved function, but the beneficial effects were small to moderate and were outweighed by a substantial increase in the risk of adverse events [247; 248]. The authors of the review concluded that opioids should not be used routinely for individuals with osteoarthritis, even for severe pain. Some guidelines suggest the use of weak narcotics or opioids for pain that has been refractory to other pharmacologic agents; however, the guidelines note that strong opioids should be used sparingly [193]. The 2021 AAOS guideline on the treatment of knee osteoarthritis emphasizes the importance of removal of oral narcotics from the medications prescribed due to the rise of the opioid epidemic in the United States [198]. The ACR guidelines conditionally recommend against using opioid analgesics for osteoarthritis of the hand [185].

  

In reviewing the literature for its guidelines on the treatment of osteoarthritis of the glenohumeral joint, the AAOS was not able to find sufficient evidence to support several pharmacologic treatments, including acetaminophen, NSAIDs, opioids, or narcotics. As a result, the AAOS states it is unable to recommend for or against the use of any of these options for the initial treatment of patients with osteoarthritis of this joint [197].

Moderate-quality evidence indicates that compared with placebo, tramadol alone or in combination with acetaminophen probably has no important benefit on mean pain or function in people with osteoarthritis, although slightly more people in the tramadol group report an important improvement (defined as 20% or more). Moderate-quality evidence shows that adverse events probably cause substantially more participants to stop taking tramadol. The increase in serious adverse events with tramadol is less certain, due to the small number of events [249].

### Topical Analgesics

There is good evidence that topical NSAIDs have efficacy comparable to oral NSAIDs, although most trials have involved knee osteoarthritis only, and head-to-head trials have not been large enough to evaluate the comparative risk of serious cardiovascular events and gastrointestinal effects [200]. There is also good evidence that topical NSAIDs are safer than oral NSAIDs, but a systematic literature review showed that systemic adverse events have occurred in a substantial proportion of older adults treated with topical NSAIDs [250]. Capsaicin has also been effective in relieving osteoarthritis-related pain, and some guidelines have suggested the use of this topical agent as an alternative treatment or an adjunct to treatment with oral analgesics [193]. The ACR guideline recommends against the use of topical capsaicin for hand osteoarthritis and for topical NSAIDs for hand and knee osteoarthritis [185]. The AHRQ comparative review found that topical capsaicin was superior to placebo but associated with increased local adverse events and withdrawals due to adverse events [200].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American College of Rheumatology and the Arthritis Foundation conditionally recommend against topical capsaicin in patients with hand osteoarthritis.

(https://www.rheumatology.org/Portals/0/Files/Osteoarthritis-Guideline-Early-View-2019.pdf. Last accessed September 22, 2022.)

**Strength of Recommendation:** Conditional against

As is the case for oral analgesics, the AAOS was not able to find sufficient evidence to support the use of topical analgesics for the treatment of glenohumeral joint osteoarthritis and is unable to recommend for or against the use of these agents for the initial treatment of patients with osteoarthritis of that joint [197].

### Intra-Articular Corticosteroids

Most of the evidence regarding the efficacy of intra-articular injection of long-acting corticosteroids comes from the literature on osteoarthritis of the knee, and many experts have called for more research on this treatment approach at the hip and other joints [35; 223]. In general, this treatment option is used for moderate-to-severe pain in a joint that has not responded to nonpharmacologic measures or to oral analgesics. Pain relief is thought to be related to the anti-inflammatory effects of the corticosteroid [251; 252].

Certain guidelines conditionally recommend intra-articular injection of corticosteroids into the knee or hip, especially after aspiration of fluid in patients who have signs of local inflammation with joint effusion [9; 185; 206]. For example, the ACR recommends this therapy for knee and hip osteoarthritis if the patient does not have satisfactory response to acetaminophen and topical NSAIDs and if there is a contraindication to oral NSAIDs. The AAOS provides a moderate recommendation for the use of intra-articular corticosteroid therapies. Extended release agents are recommended over immediate release to improve patient outcomes [198].]. Although the approach is otherwise widely recommended, it is acknowledged that intra-articular corticosteroids provide short-term relief only [35; 253; 254]. A meta-analysis of 28 trials (1,973 patients) of knee osteoarthritis showed a benefit of pain relief for two to four weeks, with no benefit in terms of functional improvement and no benefit in either pain or function beyond four weeks [253]. An update to the meta-analysis, which included 27 trials (1,767 patients), found that the overall quality of the evidence did not clearly support a benefit of intra-articular corticosteroid use after one to six weeks [254]. Despite the short-term benefit found in most studies, clinical experience has shown longer relief in many patients [35]. Because of the potential side effects of intra-articular injections, which include long-term damage to joint cartilage, flare after injection, and infection, most physicians do not recommend more than three to four injections per joint per year [9; 35]. Intra-articular injection is more technically difficult in the hip joint than in the knee, and radiographic or ultrasonographic guidance has been suggested, although there are no comparative data to provide evidence that accuracy is increased with such guidance [9; 223].

Recommendations for the use of intra-articular corticosteroids at other joints are based primarily on expert opinion, as randomized controlled trials are lacking or have included small numbers of patients. EULAR guidelines for osteoarthritis of the hand note that intra-articular corticosteroids are effective for painful flares of osteoarthritis, especially of the trapeziometacarpal joint [178]. As with data on the hip and knee, intra-articular injections have provided benefit for up to four weeks [9; 178].

Although intra-articular corticosteroids are often used in clinical practice to treat shoulder pain of all etiologies, the AAOS concluded that there was insufficient evidence to support the use of this approach for the treatment of osteoarthritis of the glenohumeral joint [197]. Intra-articular corticosteroids are also options for refractory pain in individuals with osteoarthritis of the elbow or ankle, although data are lacking to support the approach [31; 32; 58].

**Intra-Articular Hyaluronan (Viscosupplementation)**

Endogenous hyaluronan (also known as hyaluronic acid) is a primary component of the extracellular matrix of synovial membrane and tissue and articular cartilage, as well as the synovial fluid [255]. It provides viscoelasticity and lubrication to the joint and helps to maintain tissue hydration. The use of exogenous hyaluronan to treat osteoarthritis—known as viscosupplementation—began in the 1960s; several formulations of viscosupplements are now available, each produced by different manufacturers with different molecular weights. Data on comparison of high-molecular-weight and low-molecular-weight hyaluronic acid have been conflicting, with some studies indicating that high-molecular-weight hyaluronic acid is more effective, whereas other analyses have shown that the efficacy is similar [256; 257]. Research reviewed by the AAOS panel suggests that high-molecular-weight hyaluronic acid is more effective than low-molecular-weight [198]. The AAOS guideline does not recommend hyaluronic acid for routine use in the treatment of symptomatic knee osteoarthritis [198]. How hyaluronan and similar products alleviate osteoarthritis-related symptoms is not entirely clear, but its action is thought to be related to its anti-inflammatory, anabolic, and chondroprotective properties [71; 258].

It is difficult to determine the efficacy of hyaluronan because research evidence is confounded by different molecular weights of hyaluronan preparations, different dosing schedules, and poor trial design, and the level of evidence across studies has been low [223; 255; 256; 259]. Most of the evidence available is related to osteoarthritis of the knee, with limited data available on use of the treatment for osteoarthritis of the hip, hand, or shoulder.

Since the publication of the 2000 ACR guidelines, certain studies and analyses have supported the efficacy of hyaluronan/hylan derivatives for relieving pain and improving function in patients with symptomatic osteoarthritis of the knee (compared with placebo), with the greatest benefit found in conjunction with less severe pain and disability at 5 to 13 weeks after injection [206; 256; 260; 261]. However, researchers have noted that the effect size is small compared with placebo and that the effect may be overestimated as a result of publication bias [255; 256; 262]. When compared with NSAIDs, hyaluronan takes longer to relieve knee symptoms; additionally, the dosing schedule necessitates more office visits than intra-articular corticosteroids, creating inconvenience and increasing costs [206; 223]. Uncontrolled and small studies of hyaluronic acid for hip osteoarthritis have shown pain reduction after treatment, but intra-articular corticosteroids were more effective in one small study [223; 259; 263].

In its 2019 recommendations, the ACR conditionally recommends against using intra-articular therapies for hand osteoarthritis [185]. This recommendation is based largely on the absence of evidence from randomized controlled trials to support the benefits as well as the potential for harm from such therapy [185].

In its 2021 guideline on the treatment of osteoarthritis of the knee, the AAOS notes that it cannot recommend the use of intra-articular hyaluronic acid for individuals with symptomatic disease [198]. The rationale for this recommendation is based on a lack of efficacy, not potential harm. Treatment with hyaluronan has been reported to be well tolerated, with a low incidence of adverse events [259; 260; 264]. Among the potential adverse events are transient pain (mild to moderate) at the injection site and increases in joint pain and/or swelling [71]. The NICE guidelines, revised in 2014, also note that intra-articular injections of hyaluronan cannot be recommended for the treatment of osteoarthritis [199; 255].

Evidence of benefit of hyaluronan for osteoarthritis of other joints is limited. A small study (56 patients) showed that a single course of three injections of intra-articular sodium hyaluronate relieved pain and improved joint function in patients with osteoarthritis of the carpometacarpal joint of the thumb. Although the effects were achieved more slowly than treatment with triamcinolone, the duration of benefit was longer (up to six months) [265]. In another small study (16 men), intra-articular sodium hyaluronate (administered once weekly for five weeks) improved scores for pain (primarily at rest) related to osteoarthritis of the trapeziometacarpal joint [178].

  

The AAOS recommends viscosupplementation as an option for patients with glenohumeral joint osteoarthritis but notes that the level of evidence for the recommendation is weak [197]. A case series of 18 patients with post-traumatic osteoarthritis of the elbow demonstrated short-term pain relief and very limited improvement in function, and the authors concluded that viscosupplementation was not suitable for the condition [266]. Descriptions of suggested treatment options for osteoarthritis of the ankle have not included hyaluronan, although a review of seven studies (275 patients) published between 2006 and 2008 suggested that viscosupplementation may be of benefit for osteoarthritis at that joint [267].

## ALTERNATIVE THERAPIES

### Glucosamine and/or Chondroitin Sulfate

In the United States, glucosamine and chondroitin are heavily marketed as dietary supplements that promote "joint health" and relieve the symptoms of osteoarthritis of the knee and hip. Glucosamine and chondroitin are both made in the body; glucosamine is an amino sugar that is thought to enhance the formation and repair of cartilage, and chondroitin is a carbohydrate found in cartilage that is thought to promote water retention and elasticity and to inhibit the enzymes that degrade cartilage. More than 20 products contain glucosamine alone, chondroitin alone, or a combination of the two, and contamination or mislabeling has been found for some products [268].

Data on the efficacy of glucosamine and chondroitin are available primarily for osteoarthritis of the knee, with limited data on its effectiveness for osteoarthritis of the hip; no studies have been done to evaluate the use of these supplements for osteoarthritis at other joint sites. Several early systematic reviews failed to show a benefit of glucosamine and/or chondroitin in terms of pain, stiffness, and function when compared with placebo [223; 269]. These findings were supported by the results of the Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT), a randomized study involving 1,583 patients with symptomatic knee osteoarthritis that has provided the best evidence to date on these supplements [201; 270]. The results demonstrated that glucosamine and chondroitin sulfate, alone or in combination, did not reduce pain more effectively than placebo [270]. A multicenter study done as part of GAIT showed that the combination of glucosamine and chondroitin sulfate did not alter progression of knee osteoarthritis, with no clinically important difference in the loss of joint space width compared with placebo [271]. A report on the two-year results from GAIT noted that there were no significant differences in pain among groups treated with glucosamine, chondroitin sulfate, a combination of the two supplements, or a placebo [272].

A systematic review evaluated the benefit and harm of chondroitin compared with placebo or a comparable oral medication (e.g., NSAIDs, analgesics, opioids, glucosamine) [273]. The review included 43 randomized controlled trials, including 4,962 participants treated with chondroitin and 4,148 participants given placebo or another control. The majority of trials were in osteoarthritis of the knee, with few in the hip or hand, and the length of the trials varied from one month to three years. In studies of less than six months in length, participants treated with chondroitin achieved significantly better pain scores than those given placebo (absolute risk difference: 10% lower); the risk difference for pain was 9% lower in studies longer than six months. A 20% reduction in knee pain was achieved by 53 of 100 participants in the chondroitin group versus 47 of 100 in the placebo group. Differences in the composite of pain, function, and disability favored chondroitin compared with placebo in studies of less than six months. Chondroitin was associated with significantly lower odds of serious adverse events compared with placebo. Chondroitin alone or in combination with glucosamine or another supplement is associated with a significant reduction in pain compared with placebo or an active control; no significant differences in the numbers of adverse events were reported. As stated, the authors found that most of the randomized trials included were of low quality; overall, the benefit of chondroitin was small to moderate [273]. Other analyses and results of randomized controlled trials have indicated that glucosamine and/or chondroitin sulfate have no or modest benefit in terms of pain, function, or structural alterations [274; 275; 276].

In its guidelines on the management of osteoarthritis of the hand, knee, and hip, the ACR deems the evidence on glucosamine and chondroitin to be inconclusive and conditionally recommends against their use [185]. The 2021 AAOS guideline on the management of knee osteoarthritis suggests that glucosamine and/or chondroitin may be helpful in reducing pain and improving function for patients with mild-to-moderate knee osteoarthritis; however, the evidence is inconsistent and limited, and additional research clarifying the efficacy of each supplement is needed [198]. With regard to osteoarthritis of the glenohumeral joint, the AAOS is not able to recommend for or against the use of glucosamine and/or chondroitin [197].

### Other Products

In a systematic review undertaken to evaluate the effectiveness of 22 herbal medicinal products, there was some evidence of pain relief with topical capsaicin, avocado-soybean unsaponifiables, and SKI306X (a Chinese herbal mixture). However, none of the 22 products had proof of effectiveness beyond doubt [277]. According to a review of studies involving antioxidant and anti-inflammatory supplements, the following cannot be recommended for the treatment of osteoarthritis: vitamin E (alone); a combination of vitamins A, C, and E; ginger; turmeric; omega-3 fatty acids; or Zyflamend (an extract of 10 different herbs) [278]. Additional clinical trials are needed before alternative supplements can be recommended.

## OPERATIVE TREATMENT

Operative treatment for osteoarthritis should be delayed until all possible nonoperative options have been exhausted [19]. In general, the indications for operative treatment are debilitating pain and major limitations in function and activities of daily living [19; 185].

In an effort to delay total knee or hip replacement, many have recommended arthroscopic lavage and debridement, but several studies, systematic reviews, and meta-analyses have shown that there is no evidence to support the efficacy of this approach for treatment of osteoarthritis of the knee [279; 280; 281; 282]. In addition, comparisons between the use of intra-articular corticosteroids and joint lavage showed no differences between the two treatments with respect to efficacy or safety [198; 253; 254]. Arthroscopic lavage and debridement may be useful for removing unstable tissues (such as loose bodies, meniscal tears, or loose cartilage) that are causing mechanical symptoms [19; 279].

In its guideline on the management of knee osteoarthritis, the AAOS recommends against performing arthroscopy with debridement or lavage in patients with a primary diagnosis of symptomatic osteoarthritis of the knee [198]. This recommendation does not apply to patients with meniscal tear, loose body, or other mechanical derangement, with concomitant diagnosis of knee osteoarthritis [198]. It is suggested that clinical judgment, along with patient preference, should guide the consideration for meniscectomy. The AAOS found insufficient evidence on arthroscopic treatment of the glenohumeral joint and is therefore unable to recommend for or against the procedure [197].

Experts have described satisfactory outcomes after arthroscopic debridement of the elbow [31; 283]. The ideal candidate for the procedure is younger than 60 years of age, is active, and has impingement pain at the extremes of the range of motion but not at the midpoint of the arc of motion or at rest [31; 58]. Compared with open debridement, the arthroscopic procedure is associated with decreased intraoperative bleeding and less postoperative pain. The procedure is technically demanding but is safe when performed by an experienced surgeon familiar with the technique [31].

Debridement (through arthroscopy or arthrotomy) of the ankle has relieved pain, decreased swelling and stiffness, and improved the activity level in more than half of patients [32]. Improvement is most likely when debridement is done to remove osteophytes, smooth unstable chondral surfaces, and remove loose bodies [32].

The 2021 AAOS guideline on the treatment of knee osteoarthritis includes a limited recommendation for valgus-producing proximal tibial osteotomy [198]. Despite the lack of a true randomized controlled trial comparing high tibial osteotomy to nonoperative management, the studies reviewed by the AAOS workgroup all agree with the premise that pain is reduced by the procedure [198].

### Total Arthroplasty

Total arthroplasty (joint replacement) is considered when all other options have failed. Indications for the procedure are severe symptomatic disease (chronic pain and disability) [19]. The procedure has led to high rates of good-to-excellent results when done at the knee and hip and is cost-effective compared with nonoperative management [19; 38].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the National Collaborating Centre for Chronic Conditions, referral for joint replacement surgery should be considered for people with osteoarthritis who experience joint symptoms (pain, stiffness and reduced function) that have a substantial impact on their quality of life and are refractory to non-surgical treatment. Referral should be made before there is prolonged and established functional limitation and severe pain.

(https://www.nice.org.uk/guidance/cg177. Last accessed September 22, 2022.)

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

#### *Knee Arthroplasty*

In 2018, an estimated 715,203 total knee arthroplasties were completed in the United States [284]. According to the National Institutes of Health, the success of total knee arthroplasty in most patients is strongly supported by more than 20 years of follow-up data, with significant improvement in pain, joint function, and quality of life in 90% of patients [285]. However, some patients will experience prosthesis failure, and risk factors for failure include male gender, age younger than 55 years at the time of surgery, obesity, and the presence of comorbidities. In terms of factors related to the surgeon, greater procedure volume (both of the surgeon and the facility), prosthesis choice, and surgical technique (e.g., proper alignment of the prosthesis) all contribute to better patient outcomes [285]. It is important to note that both knee and hip arthroplasty are associated with a high risk of deep vein thrombosis (DVT) and pulmonary embolism compared with other surgeries. Without prophylaxis, DVT will develop in most patients [286]. Therefore, prophylactic treatment, usually with either low-molecular-weight heparin or warfarin, is recommended for patients undergoing one of these procedures, unless contraindications are present.

Because there are anatomic differences in joint structure and size between men and women, a gender-specific knee prosthesis was designed specifically for women [287]. Researchers believed that the better fit would lead to improvements in recovery and outcomes for women who had total knee arthroplasty. In one

  

study, 85 women who received a standard joint in one knee and the gender-specific joint in the other knee were followed up for two years after the surgery [287]. Patient satisfaction, range of motion while lying, and WOMAC scores were similar for both prostheses. The researchers did note that the standard prostheses appeared to fit at the distal part of the femur better than the gender-specific type; furthermore, the small size of the gender-specific prosthesis exposed more bone and resulted in more bleeding immediately after surgery. Although the study concluded that there were no benefits to the use of gender-specific prostheses in women undergoing total knee arthroplasty, research evaluating long-term effects is necessary.

Postoperative rehabilitation is a necessary component of recovery after operative treatment of osteoarthritis and requires cooperation of the entire multidisciplinary team. In the case of total knee arthroplasty, patients should be guided on a postoperative exercise and rehabilitation plan that focuses on obtaining an acceptable level of joint function, range of motion, and quality of life (e.g., ability to perform activities of daily living unassisted). In some cases, a continuous passive motion device may be used. This device has been suggested as a means to obtain greater range of motion more quickly after surgery [288]. While this may be the case, no long-term benefits (e.g., ultimate range of motion) have been definitively proven, and evidence on the short-term effects are conflicting [286; 288; 289]. It is not a recommendation of the AAOS or the ACR at this time.

In general, the institution of a structured exercise plan, guided by the physician and physical therapist, will assist patients in regaining range of motion and return to performing daily activities. A daily physical therapy program after total knee arthroplasty should continue for four to six weeks, at which point the patient's needs will be reassessed. According to one study, the greatest improvements in lower-extremity functional status after total knee arthroplasty were demonstrated in the first 12 weeks, with little improvement noted after 26 weeks [290]. By the end of physical therapy, the patient should be able to perform activities of daily living and progress to ambulating on flat surfaces and stairs. Strengthening and stretching exercises focusing on the hamstrings and quadriceps should be incorporated into the program.

There is some debate regarding the importance of supervised outpatient physical therapy compared with exercise programs carried out in the patient's home. One meta-analysis of 10 randomized controlled trials found that supervised physical therapy provided no benefits for patients who were younger at the time of surgery and had few or no comorbidities [291]. However, the researchers noted that there is a lack of evidence regarding the use of outpatient physical therapy for older patients with comorbidities and those who have undergone more complicated surgeries.

One study that included older patients (60 to 79 years of age) was designed to determine the functional differences between the effects of supervised physiotherapy with a standardized home exercise program following total knee arthroplasty [292]. All patients were evaluated for joint range of motion, pain, functional status, overall quality of life, and depressive symptoms. Postoperative assessment showed a significant clinical improvement in both groups, and the authors found no significant difference between the groups in range of motion and functional status.

### *Hip Arthroplasty*

Total hip arthroplasty is also relatively common, with 599,494 procedures completed in 2018 [293]. This procedure is recommended for the treatment of osteoarthritis in older patients for whom nonsurgical interventions have been ineffective. Some data suggest that the benefit of arthroplasty of the hip is greater when done earlier in the course of disease [38]. According to one study, female gender, the presence of comorbidities, contralateral hip osteoarthritis, back pain, and poor preintervention health or mental health status were predictors of poorer outcomes and lesser improvements in quality-of-life measures after total hip arthroplasty [294].

Although steps are taken to prevent it, leg length can be altered as a result of total hip arthroplasty. It is important for the leg on the operative side to be measured and, if there is a discrepancy, corrected with the use of orthotics.

As with knee arthroplasty, individuals who have undergone total hip arthroplasty require a physical therapy and exercise regimen that will allow them to obtain the optimal level of joint function and flexibility. The goals of therapy are the same as those described for total knee arthroplasty. One consideration is when to initiate physical therapy in order to gain the most improvement, particularly considering that improvements seem to plateau after 12 to 26 weeks. In a study of 593 patients who had total hip arthroplasty (performed by six different surgeons using different surgical techniques), 191 began physical therapy on the day of surgery and the remaining 402 patients began physical therapy on postoperative day 1 [295]. The length of stay was significantly shorter for the patients who had early physical therapy (2.16 days compared with 3.38 days).

Another consideration is the type of postoperative exercise and rehabilitation program recommended. One study compared a conventional rehabilitation program with the use of early maximal strength training in patients who had received a total hip replacement [296]. Individuals in the treatment group performed leg press and abduction with the operated leg five times a week for four weeks in addition to the conventional program (supervised physical therapy three to five times per week for four weeks). The researchers found that those who included maximal strength training in their postsurgical physical therapy had a significantly larger increase in muscular strength and a trend toward a better work efficiency than those in the conventional therapy group.

### *Other Joints*

Other joint replacement procedures are not done as widely and are not associated with the same success as knee and hip arthroplasty. The AAOS guideline on the treatment of osteoarthritis of the glenohumeral joint includes a weak recommendation for total shoulder arthroplasty and hemiarthroplasty as options, with a moderate recommendation for total arthroplasty over hemiarthroplasty [197].

The use of total elbow arthroplasty is limited by the high risk for instability and loosening and is rarely used to treat primary osteoarthritis [31; 58]. When performed in younger patients, long-term success of the procedure has been limited because of high functional demands [31]. As a result, total replacement should be reserved for patients older than 65 years of age who are willing to accept low levels of activity [31; 58].

The complex anatomic and biomechanical features of the ankle joint have challenged the use of joint replacement [32]. New designs of prostheses have led to good-to-excellent outcomes postoperatively, but complications have included osteomyelitis and osteolysis. In addition, only short-term data are available.

## CONCLUSION

An estimated 30.8 million adults have osteoarthritis, making it the most common joint disorder, and this number is expected to rise as the population grows older and lives longer. The disease is a leading cause of activity limitation and absenteeism among working-age adults and is associated with a significant decline in function among older individuals. The etiology of osteoarthritis is complex and not completely understood; some experts have theorized that osteoarthritis represents distinct disease entities according to the joint site, as the risk factors and clinical presentation vary across joints. This variation, along with a lack of correlation between symptoms and radiographic evidence, has created challenges in diagnosing osteoarthritis. In addition, clinicians must consider a wide range of differential diagnoses when evaluating a patient with joint pain. Diagnostic criteria have been well-established for osteoarthritis of the most common joints (knee, hip, and hand), and evidence-based recommendations for diagnosis of the knee and hand have been published. The clinical presentation and history remain the most important components of diagnosis for osteoarthritis at most joint sites. No curative therapy is available for osteoarthritis, and management is thus focused on decreasing pain and increasing function. Evolving evidence has shown that many commonly used treatment options for osteoarthritis offer no or limited benefit. Healthcare professionals must be familiar with the available evidence-based guidelines for the management of osteoarthritis (knee, hip, hand, and shoulder) and discuss appropriate options with their patients. A shared decision-making process and a multidisciplinary approach are keys to successful management.

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

  

## COURSE TEST - #94954 OSTEOARTHRITIS

*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 September 30, 2025.***

**1. Of the following, secondary osteoarthritis occurs most often in the**
- A) *hip.*
- B) *knee.*
- C) *hand.*
- D) *shoulder.*

**2. Which of the following systemic diseases may be associated with secondary osteoarthritis of the metacarpophalangeal (MCP) joints?**
- A) *Paget disease*
- B) *Chondrocalcinosis*
- C) *Avascular necrosis*
- D) *Calcium pyrophosphate deposition disease*

**3. According to population-based studies, the overall prevalence of symptomatic osteoarthritis of the knee is approximately**
- A) *8%.*
- B) *12%.*
- C) *16%.*
- D) *24%.*

**4. The primary component of normal adult articular cartilage is**
- A) *cytokines.*
- B) *chondrocytes.*
- C) *proteoglycans.*
- D) *extracellular matrix.*

**5. Which of the following is a characteristic of an osteoarthritic joint rather than an aging joint?**
- A) *Osteopenia*
- B) *Atrophy of the synovium*
- C) *Subchondral bone remodeling*
- D) *Loss of water content in the cartilage*

**6. Which of the following statements regarding genetic risk factors for osteoarthritis is TRUE?**
- A) *Specific genes may be involved with osteoarthritis at specific joints.*
- B) *There is a strong genetic predisposition for osteoarthritis of the ankle.*
- C) *Three genes have been confirmed as being responsible for osteoarthritis.*
- D) *The familial risk factor for osteoarthritis of the knee, hip, and hand has ranged from 70% to 80%.*

**7. Which of the following is the most important modifiable risk factor for severe osteoarthritis of the knee?**
- A) *Trauma/injury*
- B) *Level of activity*
- C) *Muscle weakness*
- D) *Overweight/obesity*

**8. Which of the following is NOT among the general differential diagnosis of osteoarthritis?**
- A) *Bursitis*
- B) *Infection*
- C) *Malalignment*
- D) *Overuse syndromes*

**9. Ancillary testing should be done for patients who have**
- A) *joint pain at night.*
- B) *joint line tenderness.*
- C) *family history of osteoarthritis.*
- D) *stiffness of the joint after inactivity.*

**10. The strongest sign of hip osteoarthritis on physical examination is**
- A) *crepitus.*
- B) *instability.*
- C) *gait abnormality.*
- D) *pain on internal or external rotation.*

*Test questions continue on next page* ➞

**11. Which of the following statements about diagnosis of osteoarthritis of the hand is TRUE?**

A) *Radiographic findings are an established diagnostic criterion.*
B) *The joint at the base of the thumb is not usually affected by osteoarthritis.*
C) *Osteoarthritis of the hand usually affects all of the joints in one or both hands.*
D) *Heberden and Bouchard nodes are the most characteristic clinical finding.*

**12. A hallmark feature of osteoarthritis of the ankle is**

A) *pain at rest.*
B) *previous infection.*
C) *history of ankle fracture.*
D) *malalignment of the foot.*

**13. In its guideline for the treatment of osteoarthritis of the knee, the American Academy of Orthopaedic Surgeons recommends achieving and/or maintaining a BMI less than or equal to**

A) *20.*
B) *25.*
C) *30.*
D) *35.*

**14. Which of the following is a contraindication to an exercise program for osteoarthritis?**

A) *Severe pain*
B) *Unstable angina*
C) *Age older than 80*
D) *Multiple comorbidities*

**15. Which of the following statements regarding the pharmacologic treatment of osteoarthritis is TRUE?**

A) *No evidence has been found to support the use of capsaicin.*
B) *The benefits of opioids for osteoarthritis-related pain outweigh the risks.*
C) *Nonsteroidal anti-inflammatory drugs (NSAIDs) should be prescribed at the lowest effective dose.*
D) *Cyclooxygenase-2 (COX-2)-selective NSAIDs are more effective than nonselective NSAIDs.*

**16. According to the American Academy of Orthopaedic Surgeons, there is insufficient evidence to recommend oral analgesics for osteoarthritis of the**

A) *hip.*
B) *ankle.*
C) *elbow.*
D) *shoulder.*

**17. Guidelines recommend intra-articular corticosteroids for hip and knee osteoarthritis, especially for patients with**

A) *osteophytes.*
B) *loose bodies.*
C) *persistent stiffness.*
D) *joint effusion when oral and topical treatments are contraindicated or ineffective.*

**18. Studies have shown that intra-articular corticosteroids provide pain relief for up to**

A) *four weeks.*
B) *eight weeks.*
C) *three months.*
D) *six months.*

**19. Which of the following herbal products has proof of effectiveness in the treatment of osteoarthritis?**

A) *Ginger*
B) *Tumeric*
C) *Vitamin E*
D) *None of the above*

**20. Which of the following statements regarding the surgical treatment of osteoarthritis is TRUE?**

A) *Total arthroplasty of the elbow should be reserved for older patients.*
B) *Arthroscopic treatment is not recommended for osteoarthritis of the shoulder.*
C) *The benefit of arthroplasty of the hip may be better when it is done later in the course of disease.*
D) *Gender-specific prostheses have been shown to improve outcomes in women undergoing total knee arthroplasty.*

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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## MEDICAL ETHICS FOR PHYSICIANS

**#47174 • 5 Credits**

**Book By Mail – $38 • ONLINE – $30**

**Purpose**: The purpose of this course is to briefly review the history, theory, and practical application of ethical principles to issues that arise in clinical practice. The goals of the course are to heighten awareness and promote self-reflection, address knowledge gaps, improve communication and decision-making skills, and promote reasonable, humane care for patients and families.
**Faculty**: John M. Leonard, MD; Michele Nichols, RN, BSN, MA
**Audience**: This course is designed for physicians and interested healthcare professionals.
**Additional Approvals**: ABIM, ABS, ABA, ABP, ABPath

## ISCHEMIC STROKE

UPDATE

**#90284 • 10 Credits**

**Book By Mail – $68 • ONLINE – $60**

**Purpose**: The early identification and management of the risk factors for ischemic stroke can lead to substantial health benefits and reductions in cost. However, research has documented gaps between healthcare professionals' knowledge and practice with respect to prevention, demonstrating that adherence to evidence-based or guideline-endorsed recommendations pertaining to all interventions for primary and secondary prevention are underutilized or ineffective. The purpose of this course is to provide needed information about the roles of diagnosis and screening, timely evaluation of individuals with suspected stroke, immediate treatment of stroke, and the elements of effective rehabilitation programs so that healthcare professionals may implement the necessary interventions appropriately.
**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

## HIPAA PRIVACY AND SECURITY

NEW!

**#91140 • 5 Credits**

**Book By Mail – $38 • ONLINE – $30**

**Purpose**: The purpose of this course is to provide information that will allow health and mental health professionals to more easily comply with the Privacy and Security Rules defined by HIPAA.
**Faculty**: Carol Shenold, RN, ICP
**Audience**: This course is designed for all members of the interprofessional healthcare team.
**Additional Approvals**: ABIM, ABS, ABA, ABP, ABPath

## SAFE HANDLING OF HAZARDOUS MEDICATIONS

NEW!

**#91380 • 2.5 Credits**

**Book By Mail – $23 • ONLINE – $15**

**Purpose**: Many medications require special handling to avoid hazardous exposure. The purpose of this course is to provide healthcare professionals with the knowledge and skills necessary to safely handle and administer potentially hazardous drugs.
**Faculty**: Latousha (Tasha) P. Jackson, PharmD, BCPS, QP503A
**Audience**: This course is designed for members of the healthcare team involved in receiving, handling, and administering hazardous medications.
**Additional Approvals**: ABIM, ABS, ABA

## CONTRACEPTION

UPDATE

**#93113 • 5 Credits**

**Book By Mail – $38 • ONLINE – $30**

**Purpose**: Newer contraceptive methods and new techniques for old methods (such as hysteroscopic sterilization) are attractive to patients, and their contraceptive provider (or referring provider) should have a grasp of the wide range of options. The purpose of this course is to provide healthcare professionals with the information necessary to advise patients and prescribe effective and appropriate contraceptives.
**Faculty**: Julie Quinn, MD
**Audience**: This course is designed for gynecologists, primary care physicians, nurse practitioners, and other primary care health providers, such as pharmacists, physician assistants, and nurses, who care for women of childbearing age.
**Additional Approvals**: ABIM, ABS, ABP

## NECK PAIN IN ADULTS

**#94131 • 10 Credits**

**Book By Mail – $68 • ONLINE – $60**

**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

# Course Availability List *(Cont'd)*

## VIRAL SEXUALLY TRANSMITTED INFECTIONS

**#94182 • 5 Credits**

**Book By Mail – $38 • ONLINE – $30**

**Purpose**: The purpose of this course is to enhance clinician knowledge regarding the most common viral sexually transmitted infections in order to ensure that diagnosis and treatment is initiated early, when transmission risk can be minimized.

**Faculty**: Mark Rose, BS, MA, LP

**Audience**: This course is designed for physicians, physician assistants, nurses, pharmacists, and allied health professionals involved in the care of patients at risk for or with viral sexually transmitted infections.

**Additional Approvals**: ABIM, ABS, ABP

## MALARIA AND THE INTERNATIONAL TRAVELER

**#94364 • 3 Credits**

Trending

**Book By Mail – $26 • ONLINE – $18**

**Purpose**: Malaria poses a particularly serious threat to U.S. travelers to endemic regions, and delayed diagnosis is a leading cause of death among patients with malaria in the United States. The purpose of this course is to provide healthcare professionals with the information necessary to accurately identify, treat, and educate patients regarding the risks of malaria in order to protect those who may be exposed to the disease.

**Faculty**: Richard A. Ade, RN, MPH

**Audience**: This course is designed for healthcare professionals involved in the care of persons traveling to or from areas where malaria transmission is common.

**Additional Approvals**: ABIM, ABS

## HIV/AIDS: UPDATE FOR FLORIDA

**#94723 • 1 Credit**

FL Mandate

**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

## ANIMAL-RELATED HEALTH RISKS

**#94924 • 15 Credits**

**Book By Mail – $98 • ONLINE – $90**

**Purpose**: The purpose of this course is to increase the awareness of zoonotic diseases and their management in both prevention and care. There are many potential diseases that can spread from animals to humans, and with basic precautions, most zoonoses are preventable or at least avoidable. The public has many misconceptions about what to do after a potential exposure to a zoonotic source, and healthcare professionals are often the first to help and answer questions.

**Faculty**: Sharon Holt, DVM, MBA, ADN

**Audience**: This course is designed for physicians, nurses, and allied health staff involved in identifying, treating, and preventing zoonotic diseases, including West Nile virus, Lyme disease, and avian influenza.

**Additional Approvals**: ABIM, ABS, ABP

## SUBSTANCE USE DISORDERS AND PAIN MANAGEMENT: MATE ACT TRAINING

**#95300 • 8 Credits**

MATE Act Training

**Book By Mail – $56 • ONLINE – $48**

**Purpose**: The purpose of this course is to provide clinicians who prescribe or distribute controlled substances with an appreciation for the complexities of managing patients with substance use disorders and comorbid pain in order to provide the best possible patient care and to prevent a growing social problem.

**Faculty**: Mark Rose, BS, MA, LP

**Audience**: This course is designed for all healthcare professionals who may alter prescribing practices or intervene to help meet the needs of patients with substance use disorders.

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

## ALZHEIMER DISEASE

**#96154 • 15 Credits**

UPDATE

**Book By Mail – $98 • ONLINE – $90**

**Purpose**: 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.

**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
**#96213 • 5 Credits**

**Book By Mail – $38 • ONLINE – $30**

**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, ABPath

## DEPRESSION AND SUICIDE
UPDATE

**#96404 • 15 Credits**

**Book By Mail – $98 • ONLINE – $90**

**Purpose**: Although contact with the primary care setting represents a potential opportunity for timely identification and intervention, abundant evidence indicates that many patients with depression are inadequately diagnosed and treated in these settings. The purpose of this course is to provide the information and encouragement necessary to allow primary care providers to properly diagnose, treat, and follow-up with patients with depression.
**Faculty**: Mark Rose, BS, MA, LP
**Audience**: This course is designed for physicians, nurses, physician assistants, social workers, therapists, and counselors in the primary care setting who may identify and treat patients who are depressed and/or suicidal.
**Additional Approvals**: ABIM, ABS, ABP, ABPath

## ANXIETY DISORDERS IN OLDER ADULTS
**#96690 • 3 Credits**

**Book By Mail – $26 • ONLINE – $18**

**Purpose**: Older adults are the fastest growing demographic in the world, and anxiety disorders are the most common mental disorder in this age group. The purpose of this course is to provide clinicians with the knowledge and skills necessary in order to improve the assessment and treatment of anxiety disorders in older adults.
**Audience**: This course is designed for the benefit of a broad range of allied health professionals, including but not limited to physicians, nurses, medical assistants, and nursing home administrators.
**Additional Approvals**: ABIM, ABS

## IMPLICIT BIAS IN HEALTH CARE
**#97000 • 3 Credits**

**Book By Mail – $26 • ONLINE – $18**

**Purpose**: The purpose of this course is to provide healthcare professionals an overview of the impact of implicit biases on clinical interactions and decision making.
**Audience**: This course is designed for the interprofessional healthcare team and professions working in all practice settings.
**Additional Approvals**: ABIM, ABS, ABA, ABP, ABPath

## CANNABINOID OVERVIEW
NEW!

**#98010 • 3 Credits**

**Book By Mail – $26 • ONLINE – $18**

**Purpose**: The purpose of this course is to provide healthcare professionals in all practice settings the knowledge necessary to increase their understanding of the various cannabinoids.
**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

## THE SCOOP ON COLLAGEN
NEW!

**#98070 • 1.5 Credits**

**Book By Mail – $23 • ONLINE – $15**

**Purpose**: The purpose of this course is to provide healthcare professionals in all practice settings the knowledge necessary to increase their understanding of the various collagen products.
**Faculty**: Chelsey McIntyre, PharmD
**Audience**: This course is designed for healthcare professionals whose patients are taking or are interested in taking collagen products.
**Additional Approvals**: ABIM, ABS

## HERBAL MEDICATIONS: AN EVIDENCE BASED REVIEW
**#98394 • 10 Credits**

**Book By Mail – $68 • ONLINE – $60**

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

# Course Availability List *(Cont'd)*

## CHRONIC PAIN SYNDROMES: CURRENT CONCEPTS AND TREATMENT STRATEGIES

**#98703 • 15 Credits**

**Book By Mail – $98 • ONLINE – $90**

**Purpose**: Chronic pain imposes a distressing sensory and emotional experience on the patient and potentially leads to life-altering negative outcomes. The purpose of this course is to provide clinicians with the information necessary to identify and appropriately manage chronic pain syndromes in accordance with evidence-based guidelines.
**Faculty**: Mark Rose, BS, MA, LP
**Audience**: This course is designed for physicians, nurses, physician assistants, and allied care providers in the primary care setting who may identify and treat patients with chronic pain syndromes.
**Additional Approvals**: ABIM, ABS, ABA

## PARKINSON DISEASE

**#98772 • 10 Credits**

**Book By Mail – $68 • ONLINE – $60**

**Purpose**: The purpose of this course is to provide physicians, nurses, and other members of the interprofessional healthcare team a review of pathogenesis, disease progression, diagnosis, and management of Parkinson disease, in order to improve patient care and quality of life.
**Audience**: This course is designed for all healthcare providers in the primary care setting who may encounter patients with Parkinson disease.
**Additional Approvals**: ABIM, ABS, ABPath

## OSTEOPOROSIS: DIAGNOSIS AND MANAGEMENT

**#99143 • 5 Credits**

UPDATE

**Book By Mail – $38 • ONLINE – $30**

**Purpose**: To appropriately prevent, diagnose, and treat osteoporosis, physicians and other healthcare providers should understand the epidemiology, physiology, and management. The purpose of this course is to provide members of the interdisciplinary team, including physicians, nurses, and other healthcare professionals, with the information regarding causes and treatment of osteoporosis necessary to effectively provide patient-centered care.
**Faculty**: John J. Whyte, MD, MPH; Peter Peraud, MD
**Audience**: This course is designed for members of the healthcare interdisciplinary team, especially those working with patients who present with suspected osteoporosis.
**Additional Approvals**: ABIM, ABS

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PART 2 MOC THE AMERICAN BOARD of PEDIATRICS

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MOCA™

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

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

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**#91334 MEDICAL ERROR PREVENTION AND ROOT CAUSE ANALYSIS—2 CREDITS**

Please refer to page 14.

*Expiration Date: 08/31/25* *May be taken individually for $15*

| | A | B | C | D | | A | B | C | D |
|---|---|---|---|---|---|---|---|---|---|
| 1. | ❍ | ❍ | ❍ | ❍ | 6. | ❍ | ❍ | ❍ | ❍ |
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| 3. | ❍ | ❍ | ❍ | ❍ | 8. | ❍ | ❍ | ❍ | ❍ |
| 4. | ❍ | ❍ | ❍ | ❍ | 9. | ❍ | ❍ | ❍ | ❍ |
| 5. | ❍ | ❍ | ❍ | ❍ | 10. | ❍ | ❍ | ❍ | ❍ |

**#97923 DOMESTIC VIOLENCE: THE FLORIDA REQUIREMENT—2 CREDITS**

Please refer to page 26.

*Expiration Date: 07/31/25* *May be taken individually for $15*

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

**#45121 STRATEGIES FOR APPROPRIATE OPIOID PRESCRIBING: THE FLORIDA REQ.—2 CREDITS**

Please refer to page 44.

*Expiration Date: 08/31/24* *May be taken individually for $15*

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

**#96102 FRONTOTEMPORAL DEMENTIA—2 CREDITS**

Please refer to pages 56–57.

*Expiration Date: 10/31/24* *May be taken individually for $15*

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

**#96790 PSYCHEDELIC MEDICINE AND INTERVENTIONAL PSYCHIATRY—10 CREDITS**

Please refer to pages 87–88.

*Expiration Date: 06/30/25* *May be taken individually for $60*

| | 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. | ❍ | ❍ | ❍ | ❍ |

**#94954 OSTEOARTHRITIS—10 CREDITS**

Please refer to pages 123–124.

*Expiration Date: 09/30/25* *May be taken individually for $60*

| | 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?
   *(Physicians should only claim credit commensurate with the extent of their participation in the activity.)*
3. Would you recommend this course to your peers?
4. Did the course content support the stated course objective?
5. Did the course content demonstrate the author's knowledge of the subject?
6. Was the course content free of bias?
7. Before completing this course, did you identify the necessity for education on the topic to improve your professional practice?
8. Have you achieved all of the stated learning objectives of this course?
9. Has what you think or feel about this topic changed?
10. Did evidence-based practice recommendations assist in determining the validity or relevance of the information?
11. Are you more confident in your ability to provide patient care after completing this course?
12. Do you plan to make changes in your practice as a result of this course content?
13. May we contact you later regarding planned changes in your practice and changes in treatment or health status of your patients as a result of this activity?

| #91334<br>2 Credits | #97923<br>2 Credits | #45121<br>2 Credits | #96102<br>2 Credits | #96790<br>10 Credits | #94954<br>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 Req. — If you answered YES to question #12, how specifically will this activity enhance your role as a member of the interdisciplinary team? _____

#45121 Strategies for Appropriate Opioid Prescribing: The Florida Req. — If you answered YES to question #12, how specifically will this activity enhance your role as a member of the interdisciplinary team? _____

#96102 Frontotemporal Dementia — If you answered YES to question #12, how specifically will this activity enhance your role as a member of the interdisciplinary team? _____

#96790 Psychedelic Medicine and Interventional Psychiatry — 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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Signature _____

*Signature required to receive continuing education credit.*

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