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CME FOR PHYSICIANS AND PHYSICIAN ASSISTANTS 2022–2023

Published by NetCE,
a TRC Healthcare Company
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Sacramento, CA 95899
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Opioid Safety: Balancing Benefits and Risks

Special Approvals

This course meets the requirements for 4 hours of opioid/controlled substance/pain management education and one hour of addiction education for the following states: AL, AK, AZ, AR, CA, CT, DE, GA, ID, IL, IN, IA, KS, KY, LA, MA, MD, ME, MI, MN, MS, NC, NE, NH, NJ, NM, NV, NY, RI, SC, TX, VA, VT, WA, WI, and WY.

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Audience

This course is designed for all physicians, osteopaths, physician assistants, pharmacy professionals, and nurses who may alter prescribing and/or dispensing practices to ensure safe 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. Outline the types of pain and effective approaches to managing different pain types.
2. Describe the Centers for Disease Control and Prevention's most recent guidelines for prescribing opioids.
3. Identify behaviors that are indicative of opioid seeking, diversion, addiction, and/or misuse.
4. Discuss federal and state laws pertaining to the prescription of controlled substances.
5. Create a plan to properly educate patients and families regarding safe opioid use.
6. Describe effects of, potential causes of, and approaches to minimize disparities in pain management.

Faculty

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

Faculty Disclosure

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

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Division Planner/Director Disclosure

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

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This activity has been designated for 5 Lifelong Learning (Part II) credits for the American Board of Pathology Continuing Certification Program.

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Special Approvals

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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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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

Healthcare professionals should know the best clinical practices in opioid prescribing, including the associated risks of opioids, approaches to the assessment of pain and function, and pain management modalities. Pharmacologic and nonpharmacologic approaches should be used on the basis of current knowledge in the evidence base or best clinical practices. Patients with moderate-to-severe chronic pain who have been assessed and treated, over a period of time, with nonopioid therapy or nonpharmacologic pain therapy without adequate pain relief, are considered to be candidates for a trial of opioid therapy [1; 2]. Initial treatment should always be considered individually determined and as a trial of therapy, not a definitive course of treatment [3].

TYPES OF PAIN AND THE ROLE OF OPIOIDS

ACUTE AND SUBACUTE PAIN

Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute (less than one month) or subacute (one to three months) 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 [2; 4].

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 [5; 6; 7].

CHRONIC PAIN

Nonpharmacologic therapy and nonopioid pharmacologic therapy are the preferred first-line therapies for chronic pain. 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.

interactive activity

View the CDC's video Prescription Opioids: Back on Track at https://youtu.be/EfojmJtnvFU. This video highlights the risks of opioids and offers some nonopioid options for chronic pain management.

Implantable intrathecal opioid infusion and/or spinal cord stimulation may be options for severe, intractable pain. Both options require that devices or ports be implanted, with associated risks. With intrathecal opioid infusion, the ability to deliver the drug directly into the spine provides pain relief with significantly smaller opioid doses, which can help to minimize side effects (e.g., drowsiness, dizziness, dry mouth, nausea, vomiting, and constipation) that can accompany systemic pain medications that might be delivered orally, transdermally, or through an IV [8]. However, use of opioid infusion has traditionally been limited to cancer pain. With spinal cord stimulation therapy, the most challenging aspect is patient selection. In order for patients to be considered for spinal cord stimulation, other options should have been ineffective or be contraindicated. Spinal cord stimulation is indicated for severe neuropathic pain persisting at least six months.

If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate. Clinicians should consider opioid therapy only if expected benefits for pain and function are anticipated to outweigh risks to the patient [2; 4].

Opioid therapy for chronic pain should be presented as a trial for a pre-defined period (e.g., ≤30 days). The goals of treatment should be established with all patients prior to the initiation of opioid therapy, including reasonable improvements in pain, function, depression, anxiety, and avoidance of unnecessary or excessive medication use [2; 9]. The treatment plan should describe therapy selection, measures of progress, and other diagnostic evaluations, consultations, referrals, and therapies.

In patients who are opioid-naïve, start at the lowest possible dose and titrate to effect. Dosages for patients who are opioid-tolerant should always be individualized and titrated by efficacy and tolerability [2; 9]. When starting opioid therapy for chronic pain, clinicians should prescribe short-acting instead of extended-release/long-acting (ER/LA) opioid formulations [2; 4].

The need for frequent progress and benefit/risk assessments during the trial should be included in patient education. Patients should also have full knowledge of the warning signs and symptoms of respiratory depression. Prescribers should carefully reassess evidence of benefits and risks when increasing the dosage to ≥50 mg morphine milligram equivalents (MME) per day. In its 2016 guideline, the CDC recommended that decisions to titrate dose to ≥90 mg MME/day should be avoided or carefully justified [2; 10]. This recommendation does not appear in the 2022 revision.

According to the American Society of Interventional Pain Physicians, before starting opioid therapy, clinicians must take certain basic steps to prevent opioid abuse: distinguish individual opioid abuse risk factors; screen patients' potential for addiction and abuse during their initial visit; categorize patients in accordance with their level of risk and implement an appropriate level of monitoring; and refrain from judgments before a thorough assessment. Combining the above strategies with point-of-care urine drug testing as a confirmatory tool have been shown to contribute significantly to the identification of inconsistencies.

(https://www.painphysicianjournal.com/current/pdf?article=NDIwNA%3D%3D&journal=103. Last accessed September 21, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

Prescribers should be knowledgeable of federal and state opioid prescribing regulations. Issues of equianalgesic dosing, close patient monitoring during all dose changes, and cross-tolerance with opioid conversion should be considered. If necessary, treatment may be augmented, with preference for nonopioid and immediate-release opioids over ER/LA opioids. Taper opioid dose when no longer needed [11].

PALLIATIVE CARE AND PAIN AT THE END OF LIFE

Unrelieved pain is the greatest fear among people with a life-limiting disease, and the need for an increased understanding of effective pain management is well-documented [12]. Although experts have noted that 75% to 90% of end-of-life pain can be managed effectively, rates of pain are high, even among people receiving palliative care [12; 13; 14; 15].

The inadequate management of pain is the result of several factors related to both patients and clinicians. In a survey of oncologists, patient reluctance to take opioids or to report pain were two of the most important barriers to effective pain relief [16]. This reluctance is related to a variety of attitudes and beliefs [12; 16]:

- Fear of addiction to opioids
- Worry that if pain is treated early, there will be no options for treatment of future pain

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

Education and open communication are the keys to overcoming these barriers. Every member of the healthcare team should reinforce accurate information about pain management with patients and families. The clinician should initiate conversations about pain management, especially regarding the use of opioids, as few patients will raise the issue themselves or even express their concerns unless they are specifically asked [17]. It is important to acknowledge patients' fears individually and provide information to help them differentiate fact from fiction. For example, when discussing opioids with a patient who fears addiction, the clinician should explain that the risk of addiction is low [12]. It is also helpful to note the difference between addiction and physical dependence.

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

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

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

Clinicians' attitudes, beliefs, and experiences also influence pain management, with addiction, tolerance, side effects, and regulations being the most important concerns [12; 14; 16; 18]. A lack of appropriate education and training in the assessment and management of pain has been noted to be a substantial contributor to ineffective pain management [16; 18]. As a result, many clinicians, especially primary care physicians, do not feel confident about their ability to manage pain in their patients [16; 18].

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

Strong opioids are used for severe pain at the end of life [13; 14]. Morphine, buprenorphine, oxycodone, hydromorphone, fentanyl, and methadone are the most widely used in the United States [19]. Unlike nonopioids, opioids do not have a ceiling effect, and the dose can be titrated until pain is relieved or side effects become unmanageable. Patients who are opioid-naïve or who have been receiving low doses of a weak opioid, the initial dose should be low, and, if pain persists, the dose may be titrated up daily until pain is controlled.

More than one route of opioid administration will be needed by many patients during end-of-life care, but in general, opioids should be given orally, as this route is the most convenient and least expensive. The transdermal route is preferred to the parenteral route, although dosing with a transdermal patch is less flexible and so may not be appropriate for patients with unstable pain [14]. Intramuscular injections should be avoided because injections are painful, drug absorption is unreliable, and the time to peak concentration is long [14].

CENTERS FOR DISEASE CONTROL AND PREVENTION OPIOID PRESCRIBING GUIDELINE

The Centers for Disease Control and Prevention (CDC) originally published Guideline for Prescribing Opioids for Chronic Pain—United States, 2016 in an effort to address an ongoing crisis of prescription opioid misuse, abuse, and overdose [2]. While these guidelines were based on the best available evidence at the time, there was some criticism that they were too focused on limiting opioid prescriptions—to the point of patients and prescribers complaining of stigma and reduced access to needed opioid analgesics. In response to this and to the availability of new evidence, the CDC published draft updates to the guideline in 2022 [4]. The updated clinical practice guideline is intended to achieve improved communication between clinicians and patients about the risks and benefits of pain treatment, including opioid therapy for pain; improved safety and effectiveness for pain treatment, resulting in improved function and quality of life for patients experiencing pain; and a reduction in the risks associated with long-term opioid therapy, including opioid use disorder, overdose, and death [4].

The 2022 clinical practice guideline includes 12 recommendations for clinicians who are prescribing opioids for outpatients 18 years of age or older with acute (duration <1 month) pain, subacute (duration of 1 to 3 months) pain, or chronic (duration of >3 months) pain outside of sickle cell disease related pain management, cancer pain treatment, palliative care, and end-of-life care. These recommendations are graded according to applicability and strength of the supporting evidence (***Table 1***).

CDC GUIDELINE RECOMMENDATION GRADING SCHEME	
Grade/Level	**Description**
Recommendation Categories	
A	Applies to all persons; most patients should receive the recommended course of action.
B	Individual decision making needed; different choices will be appropriate for different patients. Clinicians help patients arrive at a decision consistent with patient values and preferences and specific clinical situations.
Evidence Type	
1	Randomized clinical trials or overwhelming evidence from observational studies.
2	Randomized clinical trials with important limitations, or exceptionally strong evidence from observational studies.
3	Observational studies or randomized clinical trials with notable limitations.
4	Clinical experience and observations, observational studies with important limitations, or randomized clinical trials with several major limitations.
Source: [4]	*Table 1*

Each of the 12 recommendations is followed by considerations for implementation. These implementation considerations offer practical insights meant to further inform clinician-patient decision-making for the respective recommendation and are not meant to be rigidly or inflexibly followed. In addition, these five guiding principles should broadly inform implementation across recommendations:

- Acute, subacute, and chronic pain need to be appropriately and effectively treated independent of whether opioids are part of a treatment regimen.
- Recommendations are voluntary and are intended to support, not supplant, individualized, person-centered care. Flexibility to meet the care needs and the clinical circumstances of a specific patient are paramount.
- A multimodal and multidisciplinary approach to pain management attending to the physical health, behavioral health, long-term services and supports, and expected health outcomes and well-being of each person is critical.
- Special attention should be given to avoid misapplying this updated clinical practice guideline beyond its intended use or implementing policies purportedly derived from it that might lead to unintended consequences for patients.
- Clinicians, practices, health systems, and payers should vigilantly attend to health inequities, provide culturally and linguistically appropriate communication, including communication that is accessible to persons with disabilities, and ensure access to an appropriate, affordable, diversified, coordinated, and effective nonpharmacologic and pharmacologic pain management regimen for all persons.

The following sections are reprinted from the 2022 draft guideline from the CDC and may change with publication of the final guideline.

DETERMINING WHETHER OR NOT TO INITIATE OPIOIDS FOR PAIN

All patients with pain should receive treatment that provides the greatest benefits relative to risks. See Recommendation 1 for determining whether to initiate opioids for acute pain (i.e., with a duration of less than one month) and Recommendation 2 for determining whether or not to initiate opioids for subacute (i.e., with a duration of at least one month and less than three months) or chronic pain (i.e., with a duration of three months or more).

Recommendation 1

Nonopioid therapies are effective for many common types of acute pain. Clinicians should only consider opioid therapy for acute pain if benefits are anticipated to outweigh risks to the patient (recommendation category: B, evidence type: 3).

Implementation Considerations

There is an important role for opioid therapy for acute pain related to severe traumatic injuries (including crush injuries and burns), invasive surgeries typically associated with moderate-to-severe postoperative pain, and other severe acute pain when nonsteroidal anti-inflammatory drugs (NSAIDs) and other therapies are contraindicated or likely to be ineffective.

Opioids are not first-line therapy for many common acute pain conditions, including low back pain, neck pain, pain related to other musculoskeletal injuries (such as sprains,

strains, tendonitis, bursitis), pain related to minor surgeries typically associated with minimal tissue injury and only mild postoperative pain (e.g., dental extraction), dental pain, kidney stone pain, and headaches, including episodic migraine.

When diagnosis and severity of acute pain are reasonably assumed to warrant the use of opioids, clinicians should prescribe immediate-release opioids (see Recommendation 3) at the lowest dose to achieve expected effects (see Recommendation 4) and for no longer than the expected duration of pain severe enough to require opioids (see Recommendation 6).

Clinicians should maximize use of nonopioid pharmacologic (e.g., NSAIDs and/or acetaminophen) and nonpharmacologic (e.g., ice, heat, elevation, rest, immobilization and/or exercise) therapies as appropriate for the specific condition and continue these therapies as needed once opioids are discontinued.

Clinicians should prescribe and advise opioid use only as needed (e.g., hydrocodone 5 mg/acetaminophen 325 mg, one tablet not more frequently than every 4 hours as needed for pain) rather than on a scheduled basis (e.g., one tablet every 4 hours) and encourage and include an opioid taper if opioids will be taken around the clock for more than a few days (see Recommendation 6).

If patients already receiving opioids in a long-term fashion require additional medication for acute pain, nonopioid medications should be used when possible, and if additional opioids are required (e.g., for superimposed severe acute pain), they should be continued only for the duration of pain severe enough to require additional opioids, returning to the patient's baseline opioid dosage as soon as possible, including a taper to baseline dosage if additional opioids were used around the clock for more than a few days (see Recommendation 6).

Clinicians should ensure that patients are aware of expected benefits of, common and serious risks of, and alternatives to opioids before starting or continuing opioid therapy and should involve patients meaningfully in decisions about whether to start opioid therapy.

Recommendation 2

Nonopioid therapies are preferred for subacute and chronic pain. Clinicians should only consider initiating opioid therapy if expected benefits for pain and function are anticipated to outweigh risks to the patient. Before starting opioid therapy for subacute or chronic pain, clinicians should discuss with patients the known risks and realistic benefits of opioid therapy, should work with patients to establish treatment goals for pain and function, and should consider how opioid therapy will be discontinued if benefits do not outweigh risks (recommendation category: A, evidence type: 2).

Implementation Considerations

To guide patient-specific selection of therapy, clinicians should evaluate patients and establish or confirm the diagnosis.

Clinicians should use appropriate noninvasive, nonpharmacologic approaches to help manage chronic pain, such as exercise (aerobic, aquatic, and/or resistance exercises) or exercise therapy (a prominent modality in physical therapy) for back pain, fibromyalgia, and hip or knee osteoarthritis; weight loss for knee osteoarthritis; manual therapies for hip osteoarthritis; psychological therapy, spinal manipulation, low-level laser therapy, massage, mindfulness-based stress reduction, yoga, acupuncture, and multidisciplinary rehabilitation for low back pain; mind-body practices (yoga, tai chi, qigong), massage, and acupuncture for neck pain; cognitive-behavioral therapy [CBT], myofascial release massage, mindfulness practices, tai chi, qigong, acupuncture, and multidisciplinary rehabilitation for fibromyalgia; and spinal manipulation for tension headache.

Low-cost options to integrate exercise include walking in public spaces or use of public recreation facilities for group exercise. Physical therapy can be helpful, particularly for patients who have limited access to safe public spaces or public recreation facilities for exercise or have not improved with low-intensity physical exercise.

To improve pain management and reduce medication use and associated risks, health insurers and health systems should increase access to noninvasive, nonpharmacologic therapies with evidence for effectiveness.

Clinicians should review U.S. Food and Drug Administration (FDA)-approved labeling including boxed warnings and weigh benefits and risks before initiating treatment with any pharmacologic therapy.

When patients affected by osteoarthritis have an insufficient response to nonpharmacologic interventions such as exercise for arthritis pain, topical NSAIDs can be used in patients with a single or few joints near the surface of the skin (e.g., knee). In patients with osteoarthritis pain in multiple joints or incompletely controlled with topical NSAIDs, duloxetine or systemic NSAIDs can be considered.

NSAIDs should be used at the lowest dose and duration needed and should be used with caution, particularly in patients with cardiovascular comorbidities, chronic renal failure, or previous gastrointestinal bleeding.

When patients with chronic low back pain have had an insufficient response to nonpharmacologic approaches such as exercise, clinicians can consider NSAIDs or duloxetine for patients without contraindications.

Tricyclic, tetracyclic, and serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants, selected anticonvulsants (pregabalin, gabapentin enacarbil, oxcarbazepine), and capsaicin and lidocaine patches can be considered for neuropathic pain.

Duloxetine and pregabalin are FDA-approved for the treatment of diabetic peripheral neuropathy, and pregabalin and gabapentin are FDA-approved for treatment of post-herpetic neuralgia.

In patients with fibromyalgia, tricyclic (amitriptyline) and SNRI antidepressants (duloxetine and milnacipran), NSAIDs (topical diclofenac), and specific anticonvulsants (pregabalin and gabapentin) are used to improve pain, function, and quality of life. Duloxetine, milnacipran, and pregabalin are FDA-approved for the treatment of fibromyalgia.

Patients with co-occurring pain and depression might be especially likely to benefit from antidepressant medication (see Recommendation 8).

Opioids should not be considered first-line or routine therapy for subacute or chronic pain. This does not mean that patients should be required to sequentially "fail" nonpharmacologic and nonopioid pharmacologic therapy or be required to use any specific therapy before proceeding to opioid therapy. Rather, expected benefits specific to the clinical context should be weighed against risks before initiating therapy. In some clinical contexts (e.g., serious illness in a patient with poor prognosis for return to previous level of function, contraindications to other therapies, and clinician and patient agreement that the overriding goal is patient comfort), opioids might be appropriate regardless of previous therapies used. In other situations, (e.g., headache or fibromyalgia), expected benefits of initiating opioids are unlikely to outweigh risks regardless of previous nonpharmacologic and nonopioid pharmacologic therapies used.

Opioid therapy should not be initiated without consideration by the clinician and patient of an "exit strategy" to be used if opioid therapy is unsuccessful.

Before opioid therapy is initiated for subacute or chronic pain, clinicians should determine jointly with patients how effectiveness will be evaluated and establish treatment goals.

Clinicians seeing new patients already receiving opioids should establish treatment goals for continued opioid therapy. Clinicians should avoid rapid tapering or abrupt discontinuation of opioids (see Recommendation 5).

Patient education and discussion before starting opioid therapy are critical so that patient preferences and values can be understood and used to inform clinical decisions.

Clinicians should review available low-cost options for pain management for all patients, and particularly for low-income, underinsured and uninsured patients.

Clinicians should ensure that patients are aware of expected benefits of, common and serious risks of, and alternatives to opioids before starting or continuing opioid therapy and should involve patients in decisions about whether to start opioid therapy.

OPIOID SELECTION AND DOSAGE

Recommendation 3

When starting opioid therapy for acute, subacute, or chronic pain, clinicians should prescribe immediate-release opioids instead of ER/LA opioids (recommendation category: A, evidence type: 4).

Implementation Considerations

Clinicians should not treat acute pain with ER/LA opioids or initiate opioid treatment for subacute or chronic pain with ER/LA opioids, and clinicians should not prescribe ER/LA opioids for intermittent or as needed use.

ER/LA opioids should be reserved for severe, continuous pain. Some ER/LA opioids should be considered only for patients who have received certain dosages of opioids (e.g., 60 mg daily of oral morphine, 30 mg daily of oral oxycodone, or equianalgesic dosages of other opioids) of immediate-release opioids daily for at least 1 week.

When changing to an ER/LA opioid for a patient previously receiving a different immediate-release opioid, clinicians should consult product labeling and reduce total daily dosage to account for incomplete opioid cross-tolerance.

Clinicians should use additional caution with ER/LA opioids and consider a longer dosing interval when prescribing to patients with renal or hepatic dysfunction because decreased clearance of medications among these patients can lead to accumulation of drugs to toxic levels and persistence in the body for longer durations.

Although there might be situations in which clinicians need to prescribe immediate-release and ER/LA opioids together (e.g., transitioning patients from ER/LA opioids to immediate-release opioids by temporarily using lower dosages of both), in general, avoiding the use of immediate-release opioids in combination with ER/LA opioids is preferable, given the potential increased risk for adverse events, including respiratory depression and overdose.

Methadone should not be the first choice for an ER/LA opioid. Only clinicians who are familiar with methadone's unique risk profile and who are prepared to educate and closely monitor their patients, including assessing risk for QT prolongation and considering electrocardiographic monitoring, should consider prescribing methadone for pain.

Only clinicians who are familiar with the dosing and absorption properties of the ER/LA opioid transdermal fentanyl and are prepared to educate their patients about its use should consider prescribing it.

Recommendation 4

When opioids are initiated for opioid-naïve patients with acute, subacute, or chronic pain, clinicians should prescribe the lowest dosage to achieve expected effects. If opioids are continued for subacute or chronic pain, clinicians should use caution when prescribing opioids at any dosage, should carefully evaluate individual benefits and risks when considering increasing dosage, and should avoid increasing dosage above levels likely to yield diminishing returns in benefits relative to risks to patients (recommendation category: A, evidence type: 3).

Implementation Considerations

When opioids are initiated for opioid-naïve patients with acute, subacute, or chronic pain, clinicians should prescribe the lowest dosage to achieve expected effects.

For patients not already taking opioids, the lowest dose to achieve expected effects can be determined using product labeling as a starting point with calibration as needed based on the severity of pain and on other clinical factors such as renal or hepatic insufficiency (see Recommendation 8).

The lowest starting dose for opioid-naïve patients is often equivalent to a single dose of approximately 5–10 MME or a daily dosage of 20–30 MME/day.

Risks of opioid use, including risk for overdose and overdose death, increase continuously with dosage, and there is no single dosage threshold below which risks are eliminated.

If opioids are continued for subacute or chronic pain, clinicians should use caution when prescribing opioids at any dosage and should generally avoid dosage increases when possible.

Many patients do not experience benefit in pain or function from increasing opioid dosages to ≥50 MME/day but are exposed to progressive increases in risk as dosage increases. Therefore, before increasing total opioid dosage to ≥50 MME/day, clinicians should pause and carefully reassess evidence of individual benefits and risks. If a decision is made to increase dosage, clinicians should use caution and increase dosage by the smallest practical amount.

Additional dosage increases beyond 50 MME/day are progressively more likely to yield diminishing returns in benefits relative to risks to patients as dosage increases further. Clinicians should carefully evaluate a decision to further increase dosage based on individualized assessment of benefits and risks and weighing factors such as diagnosis, incremental benefits for pain and function relative to risks with previous dosage increases, other treatments and effectiveness, and patient values and preferences.

The recommendations related to opioid dosages are not intended to be used as an inflexible, rigid standard of care; rather, they are intended to be guideposts to help inform clinician-patient decision making. Further, these recommendations apply specifically to starting opioids or to increasing opioid dosages, and a different set of benefits and risks applies to reducing opioid dosages (see Recommendation 5).

Recommendation 5

For patients already receiving higher opioid dosages, clinicians should carefully weigh benefits and risks and exercise care when reducing or continuing opioid dosage. If risks outweigh benefits of continued opioid therapy, clinicians should optimize other therapies and work closely with patients to gradually taper to lower dosages or, if warranted based on the individual clinical circumstances of the patient, to appropriately taper and discontinue opioids. Unless there are indications of a life-threatening issue, such as warning signs of impending overdose (e.g., confusion, sedation, slurred speech), opioid therapy should not be discontinued abruptly, and clinicians should not abruptly or rapidly reduce opioid dosages from higher dosages (recommendation category: B, evidence type: 4).

interactive activity

View the CDC's video Tapering Opioids for Chronic Pain at https://youtu.be/89UXlpijYyE. This short video describes when and how clinicians should initiate opioid tapering and outlines ways to support patients through the process.

Implementation Considerations

Clinicians should consider tapering to a reduced opioid dosage, or tapering and discontinuing opioid therapy, and discuss these approaches with patients prior to initiating changes, when risks outweigh benefits (potentially including avoiding risks of tapering) of continued opioid therapy.

Patient agreement and interest in tapering is likely to be a key component of successful tapers.

For patients agreeing to taper to lower opioid dosages as well as for those remaining on higher opioid dosages, clinicians should establish goals with the patient for continued opioid therapy (see Recommendations 2 and 7) and maximize pain treatment with nonpharmacologic and nonopioid pharmacologic treatments as appropriate (see Recommendation 2).

Clinicians should collaborate with the patient on the tapering plan, including patients in decisions such as how quickly tapering will occur and when pauses in the taper may be warranted.

Clinicians should follow up frequently (at least monthly) with patients engaging in opioid tapering.

When opioids are reduced or discontinued, a taper slow enough to minimize symptoms and signs of opioid withdrawal (e.g., anxiety, insomnia, abdominal pain, vomiting, diarrhea, diaphoresis, mydriasis, tremor, tachycardia, or piloerection) should be used.

Tapers can be completed over several months to years depending on the opioid dosage and should be individualized based on patient goals and concerns. Longer durations of previous opioid therapy might require longer tapers.

Tapers of 10% per month or slower are likely to be better tolerated than more rapid tapers, particularly when patients have been taking opioids for longer durations (e.g., for one year or longer).

Significant opioid withdrawal symptoms can signal the need to further slow the taper rate.

At times, tapers might have to be paused and restarted again when the patient is ready and might have to be slowed once patients reach low dosages.

Tapers should not be reversed without careful assessment of benefits and risks of increasing opioid dosage or without maximizing nonopioid treatments for pain and addressing behavioral distress.

Once the smallest available dose is reached, the interval between doses can be extended.

Goals of the taper may vary—some patients might achieve discontinuation; others might attain a reduced dosage. If the clinician has determined with the patient that the ultimate goal of tapering is discontinuing opioids, opioids may be stopped when taken less frequently than once a day.

Clinicians should access appropriate expertise if considering tapering opioids during pregnancy because of possible risk to the pregnant patient and to the fetus if the patient goes into withdrawal.

Clinicians should advise patients that there is an increased risk for overdose on abrupt return to a previously prescribed higher dose, caution that it takes as little as a week to lose tolerance, provide opioid overdose education, and offer naloxone.

Clinicians should remain alert to signs of anxiety, depression, and opioid misuse or opioid use disorder (see Recommendations 8 and 12) that might be revealed by an opioid taper and provide treatment or arrange for management of these co-morbidities.

Clinicians should closely monitor patients who are unable to taper and who continue on high-dose or otherwise high-risk opioid regimens (e.g., opioids prescribed concurrently with benzodiazepines) and should work with patients to mitigate overdose risk (e.g., by providing overdose education and naloxone—see Recommendation 8).

Clinicians can use periodic and strategic motivational questions and statements to encourage movement toward appropriate therapeutic changes and functional goals.

Clinicians have a responsibility to provide or arrange for coordinated management of patients' pain and opioid-related problems, including opioid use disorder. Clinicians should not abandon patients.

Payers, health systems, and state medical boards should not use this clinical practice guideline to set rigid standards related to dose or duration of opioid therapy, and should ensure that policies based on cautionary dosage thresholds do not result in rapid tapers or abrupt discontinuation of opioids, and that policies do not penalize clinicians for accepting new patients who are using prescribed opioids for chronic pain, including those receiving high doses of opioids.

While Recommendation 5 specifically refers to patients using long-term, high-dose opioid therapy for subacute or chronic pain, many of the principles in these implementation considerations and supporting rationale, including communication with patients, pain management and behavioral support, and slower taper rates, are also relevant when discontinuing opioids in patients receiving shorter durations and/or lower dosages (see also Recommendations 6 and 7).

OPIOID DURATION AND FOLLOW-UP

Recommendation 6

When opioids are needed for acute pain, clinicians should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids (recommendation category: A, evidence type: 4).

Implementation Considerations

Nontraumatic, nonsurgical acute pain can often be managed without opioids (see Recommendation 1).

Opioids are sometimes needed for treatment of acute pain (see Recommendation 1). When the diagnosis and severity of acute pain warrant use of opioids, clinicians should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. For many common causes of nontraumatic, nonsurgical pain, when opioids are needed, a few days or less are often sufficient, and shorter courses can minimize the need to taper opioids to prevent withdrawal symptoms at the end of a course of opioids. However, durations should be individualized based on the clinical circumstances of the specific patient.

Clinicians should generally avoid prescribing additional opioids to patients "just in case" pain continues longer than expected.

For postoperative pain related to major surgery, procedure-specific opioid prescribing recommendations are available with ranges for amounts of opioids needed (based on actual use and refills and on consensus).

To minimize unintended impact on patients with an unexpectedly prolonged duration of severe acute pain, clinicians, practices, and health systems should have mechanisms in place to provide timely re-evaluation for the subset of patients who experience severe acute pain that continues longer than the expected duration to confirm or revise the initial diagnosis and to adjust management accordingly. In particular, clinicians, practices, and health systems should ensure all patients can access and afford additional evaluation and treatment, as needed, to minimize disparities across patients based on access to and affordability of care and refills.

Longer durations of opioid therapy are more likely to be needed when the mechanism of injury is expected to result in prolonged severe pain (e.g., severe traumatic injuries).

Patients should be evaluated at least every 2 weeks if they continue to receive opioids for acute pain.

If opioids are continued for a month or longer, clinicians should refer to recommendations on subacute and chronic pain for follow-up (Recommendation 7) and tapering (Recommendation 5).

If patients already receiving long-term opioids require additional opioids for superimposed severe acute pain (e.g., major surgery), opioids should be continued only for the duration of pain severe enough to require additional opioids, returning to the patient's baseline opioid dosage as soon as possible, including a taper to baseline dosage if additional opioids were used around the clock for more than a few days.

If opioids are prescribed continuously (around the clock) for more than a few days for acute pain, clinicians should prescribe a taper to minimize withdrawal symptoms on discontinuation of opioids.

Taper durations might need to be adjusted depending on the duration of the initial opioid prescription (see supporting rationale for this recommendation for additional details).

Tapering plans should be discussed with the patient prior to hospital discharge and with clinicians coordinating the patient's care as an outpatient. For tapering considerations when patients have taken opioids continuously for longer than one month, see Recommendation 5.

Recommendation 7

Clinicians should evaluate benefits and risks with patients within one to four weeks of starting opioid therapy for subacute or chronic pain or of dose escalation. Clinicians should evaluate benefits and risks of continued therapy with patients every three months or more frequently (recommendation category: A, evidence type: 4).

Implementation Considerations

In addition to evaluating benefits and risks of opioids before starting opioid therapy (see Recommendation 2), clinicians should evaluate patients to assess benefits and risks of opioids within 1 to 4 weeks of starting long-term opioid therapy or of dose escalation.

Clinicians should consider follow-up intervals within the lower end of this range when ER/LA opioids are started or increased, given increased risk for overdose within the first 2 weeks of treatment, or when total daily opioid dosage is ≥50 MME/day. (Note: Overdose risk is doubled across multiple studies for dosages of 50 to <100 MME/day relative to <20 MME/day. See Recommendation 4.)

Shorter follow-up intervals (within 3 days) should be strongly considered when starting or increasing the dosage of methadone, given the variable half-life of this drug (see Recommendation 3) and the potential for drug accumulation during initiation and during upward titration of dosage.

An initial follow-up interval closer to 4 weeks can be considered when starting immediate-release opioids at a dosage <50 MME/day.

Clinicians should regularly reassess all patients receiving long-term opioid therapy, including patients who are new to the clinician but on long-term opioid therapy, at least every 3 months.

Clinicians seeing new patients already receiving opioids should establish treatment goals for continued opioid therapy (see Recommendation 2).

Clinicians should re-evaluate patients who are at higher risk for opioid use disorder or overdose (e.g., patients with depression or other mental health conditions, a history of substance use disorder, a history of overdose, taking ≥50 MME/day, or taking other central nervous system depressants with opioids) more frequently than every 3 months.

To minimize unintended impact on patients with challenges in accessing or affording follow-up visits, practices, and health systems should work to ensure all patients can access and afford follow-up evaluation.

In practice contexts where virtual visits are part of standard care (e.g., in remote areas where distance or other context makes follow-up visits challenging), follow-up assessments that allow the clinician to communicate with and observe the patient through telehealth modalities may be conducted.

At follow-up, clinicians should review patient perspectives and goals, determine whether opioids continue to meet treatment goals, including sustained improvement in pain and function; whether the patient has experienced common or serious adverse events or early warning signs of serious adverse events or has signs of opioid use disorder.

Clinicians should ensure that treatment for depression, anxiety, or other psychological co-morbidities is optimized.

Clinicians should ask patients about their preferences for continuing opioids, given their effects on pain and function relative to any adverse effects experienced. If risks outweigh benefits of continued opioid therapy (e.g., if patients do not experience meaningful, sustained improvements in pain and function compared with prior to initiation of opioid therapy; if patients are taking higher-risk regimens [e.g., dosages ≥50 MME/day or opioids combined with benzodiazepines] without evidence of benefit; if patients believe benefits no longer outweigh risks; if patients request dosage reduction or discontinuation; or if patients experience overdose or other serious adverse events), clinicians should work with patients to reduce opioid dosage or to discontinue opioids when possible, using principles from Recommendation 5.

Clinicians should maximize pain treatment with nonpharmacologic and nonopioid pharmacologic treatments as appropriate (see Recommendation 2).

ASSESSING RISK AND ADDRESSING HARMS OF OPIOID USE

Recommendation 8

Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk for opioid-related harms and discuss with patients. Clinicians should work with patients to incorporate into the management plan strategies to mitigate risk, including offering naloxone when factors that increase risk for opioid overdose are present (recommendation category: A, evidence type: 4).

Implementation Considerations

Clinicians should offer naloxone when prescribing opioids to patients at increased risk for overdose, including patients with a history of overdose, patients with a history of substance use disorder, patients with sleep-disordered breathing, patients taking higher dosages of opioids (e.g., ≥50 MME/day), patients taking benzodiazepines with opioids (see Recommendation 11), and patients at risk for returning to a high dose to which they have lost tolerance (e.g., patients undergoing tapering or recently released from prison).

Practices should provide education on overdose prevention and naloxone use to patients and offer to provide education to members of their households.

Naloxone co-prescribing can be facilitated by clinics or practices with resources to provide naloxone training and by collaborative practice models with pharmacists or through standing orders for naloxone at pharmacies.

Resources for prescribing naloxone in primary care and emergency department settings can be found through Prescribe to Prevent at http://prescribetoprevent.org; additional resources are at https://samhsa.gov.

In part because of concerns about cost of naloxone and access for some patients, this recommendation specifies that naloxone should be "offered" to patients. Clinicians, health systems, and payers should work to ensure patients can access naloxone, a potentially lifesaving treatment.

Clinicians should avoid prescribing opioids to patients with moderate or severe sleep-disordered breathing when possible to minimize risks for opioid overdose.

When making decisions about whether to initiate opioid therapy for pain during pregnancy, clinicians and patients together should carefully weigh benefits and risks. For pregnant people already receiving opioids, clinicians should access appropriate expertise if considering tapering opioids because of possible risk to the pregnant patient and to the fetus if the patient goes into withdrawal (see Recommendation 5).

For pregnant people with opioid use disorder, medications for opioid use disorder (buprenorphine or methadone) have been associated with improved maternal outcomes and should be offered (see Recommendation 12).

Clinicians should use additional caution and increased monitoring (see Recommendation 7) to minimize risks of opioids prescribed for patients with renal or hepatic insufficiency and for patients aged ≥65 years and should implement interventions to mitigate common risks of opioid therapy among older adults, such as exercise or bowel regimens to prevent constipation, risk assessment for falls, and patient monitoring for cognitive impairment.

Clinicians should ensure that treatment for depression and other mental health conditions is optimized, consulting with behavioral health specialists when needed.

Clinicians should ask patients about their drug and alcohol use.

Clinicians should use prescription drug monitoring program (PDMP) data (see Recommendation 9) and toxicology screening (see Recommendation 10) as appropriate to assess for concurrent substance use that might place patients at higher risk for opioid use disorder and overdose.

Clinicians should provide specific counseling on increased risks for overdose when opioids are combined with other drugs or alcohol (see Recommendation 2) and ensure that patients are provided or receive effective treatment for substance use disorders when needed (see Recommendation 12).

Although substance use disorder can alter the expected benefits and risks of opioid therapy for pain, patients with co-occurring pain and substance use disorder require ongoing pain management that maximizes benefits relative to risks. See "Pain management for patients with opioid use disorder" section of Recommendation 12 for additional considerations specific to patients with pain and opioid use disorder.

If clinicians consider opioid therapy for chronic pain for patients with substance use disorder, they should discuss increased risks for opioid use disorder and overdose with patients, carefully consider whether benefits of opioids outweigh increased risks, and incorporate strategies to mitigate risk into the management plan, such as offering naloxone and increasing frequency of monitoring (see Recommendation 7).

If patients experience nonfatal opioid overdose, clinicians should evaluate for opioid use disorder and treat or arrange treatment if needed. Clinicians should work with patients to reduce opioid dosage and to discontinue opioids when indicated (see Recommendation 5) and should ensure continued close monitoring and support for patients prescribed or not prescribed opioids. If clinicians continue opioid therapy in patients with prior opioid overdose, they should discuss increased risks for overdose with patients, carefully consider whether benefits of opioids outweigh substantial risks, and incorporate strategies to mitigate risk into the management plan, such as considering offering naloxone and increasing frequency of monitoring (see Recommendation 7).

Recommendation 9

When prescribing initial opioid therapy for acute, subacute, or chronic pain, and periodically during opioid therapy for chronic pain, clinicians should review the patient's history of controlled substance prescriptions using state PDMP data to determine whether the patient is receiving opioid dosages or combinations that put the patient at high risk for overdose (recommendation category: B, evidence type: 4).

Implementation Considerations

Ideally, PDMP data should be reviewed before every opioid prescription for acute, subacute, or chronic pain. This is recommended in all jurisdictions where PDMP availability and access policies, as well as clinical practice settings, make this practicable (e.g., clinician and delegate access permitted).

At a minimum, during long-term opioid therapy, PDMP data should be reviewed before an initial opioid prescription and then every three months or more frequently. The recommendation category B acknowledges variation in PDMP availability and circumstances. However, because PDMP information can be most helpful when results are unexpected, and to minimize bias in application, clinicians should apply this recommendation when feasible to all patients rather than differentially based on assumptions about what they will learn about different patients.

Clinicians should use specific PDMP information about medications prescribed to their patient in the context of other clinical information, including their patient's history, physical findings, and other relevant testing, in order to help them communicate with and protect their patient.

Clinicians should review PDMP data specifically for prescription opioids and other controlled medications patients have received from additional prescribers to determine whether a patient is receiving high total opioid dosages or combinations (e.g., opioids combined with benzodiazepines) that put the patient at high risk for overdose.

PDMP-generated risk scores have not been validated against clinical outcomes such as overdose and should not take the place of clinical judgment. Clinicians should not dismiss patients from their practice on the basis of PDMP information. Doing so can adversely affect patient safety, could represent patient abandonment, and could result in missed opportunities to provide potentially lifesaving information (e.g., about risks of prescription opioids and overdose prevention) and interventions (e.g., safer prescriptions, nonopioid pain treatment [see Recommendations 1 and 2], naloxone [see Recommendation 8], and effective treatment for substance use disorder [see Recommendations 8 and 12]).

Clinicians should take actions to improve patient safety:

- Discuss information from the PDMP with their patient and confirm that the patient is aware of any additional prescriptions. Occasionally, PDMP information can be incorrect (e.g., if the wrong name or birthdate has been entered, the patient uses a nickname or maiden name, or another person has used the patient's identity to obtain prescriptions).
- Discuss safety concerns, including increased risk for respiratory depression and overdose, with patients found to be receiving prescription opioids from more than one clinician or receiving medications that increase risk when combined with opioids (e.g., benzodiazepines; see Recommendation 11) and offer naloxone (see Recommendation 8).
- Use extreme caution when prescribing opioids and benzodiazepines concurrently, appreciating that some patient circumstances warrant prescribing of these medications concomitantly. Clinicians should communicate with others managing the patient to discuss the patient's needs, prioritize patient goals, weigh risks of concurrent benzodiazepine and opioid exposure, and coordinate care (see Recommendation 11).
- Consider the total MME/day for concurrent opioid prescriptions to help assess the patient's overdose risk (see Recommendation 4). Buprenorphine should not be counted in the total MME/day in calculations given its opioid partial agonist properties that confer a ceiling effect on respiratory depression. If patients are found to be receiving high total daily dosages of opioids, discuss safety concerns with the patient, consider in collaboration with the patient if tapering to a safer dosage is warranted (see Recommendation 5), and offer naloxone (see Recommendation 8).

- Discuss safety concerns with other clinicians who are prescribing controlled substances for their patient. Ideally, clinicians should first discuss concerns with their patient and inform him or her that they plan to coordinate care with the patient's other clinicians to improve the patient's safety.
- Screen for substance use and discuss concerns with their patient (see Recommendations 8 and 12). If clinicians believe their patient might be diverting (sharing or selling prescription opioids and not taking them), consider toxicology testing to assist in determining whether prescription opioids can be discontinued without causing withdrawal (see Recommendations 5 and 10). A negative toxicology test for prescribed opioids might indicate the patient is not taking prescribed opioids, although clinicians should consider other possible reasons for this test result, such as false negative results or misinterpretation of results (see Recommendation 10).

Recommendation 10

When prescribing opioids for subacute or chronic pain, clinicians should consider toxicology testing to assess for prescribed medications as well as other prescribed and nonprescribed controlled substances (recommendation category: B, evidence type: 4).

Implementation Considerations

Clinicians should not dismiss patients from care based on a toxicology test result because this could constitute patient abandonment and could have adverse consequences for patient safety, potentially including the patient obtaining opioids or other drugs from alternative sources and the clinician missing opportunities to facilitate treatment for substance use disorder.

Prior to starting opioids and periodically during opioid therapy, clinicians should consider toxicology testing to assess for prescribed opioids as well as other prescription and nonprescription controlled substances that increase risk for overdose when combined with opioids, including nonprescribed and illicit opioids and benzodiazepines.

Clinicians, practices, and health systems should aim to minimize bias testing and should not apply this recommendation differentially based on assumptions about what they will learn about different patients.

Predicting risk is challenging, and currently available tools do not allow clinicians to reliably identify patients who are at low risk for substance use or substance use disorder. Rather, clinicians should consider toxicology screening results as potentially useful data, in the context of other clinical information, for all patients, and consider toxicology screening whenever its potential problems can be mitigated.

Clinicians should explain to patients that toxicology testing will not be used to dismiss patients from care and is intended to improve their safety.

Clinicians should explain expected results (e.g., presence of prescribed medication and absence of drugs, including nonprescribed controlled substances, not reported by the patient) and ask patients about use of prescribed and other drugs and whether there might be unexpected results.

Toxicology screening can be performed with a relatively inexpensive presumptive immunoassay panel that tests for opiates as a class, benzodiazepines as a class, and several nonprescribed substances.

The use of confirmatory testing can add substantial costs and should be based on the need to detect specific opioids, such as those that are being prescribed, and those that cannot be identified on standard immunoassays or on the presence of unexpected toxicology test results.

Clinicians should be familiar with the drugs included in toxicology screening panels used in their practice and should understand how to interpret results for these drugs. For example, a positive "opiates" immunoassay detects morphine, which might reflect patient use of morphine, codeine, or heroin, but does not detect synthetic opioids and might not detect semisynthetic opioids. In some cases, positive results for specific opioids might reflect metabolites from opioids the patient is taking and might not mean the patient is taking the specific opioid for which the test was positive.

Restricting confirmatory testing to situations and substances for which results can reasonably be expected to affect patient management can reduce costs of toxicology testing.

Clinicians may wish to discuss unexpected results with the local laboratory or toxicologist and should discuss unexpected results with the patient.

Discussion with patients prior to specific confirmatory testing can sometimes yield a candid explanation of why a particular substance is present or absent and obviate the need for expensive confirmatory testing on that visit. For example, a patient might explain that the test is negative for prescribed opioids because she felt opioids were no longer helping and discontinued them. If unexpected results are not explained, a confirmatory test using a method selective enough to differentiate specific opioids and metabolites (e.g., gas or liquid chromatography/mass spectrometry) might be warranted.

Clinicians should use unexpected results to improve patient safety (e.g., change pain management strategy [see Recommendation 2], carefully weigh benefits and risks of reducing or continuing opioid dosage [see Recommendation 5], re-evaluate more frequently [see Recommendation 7], offer naloxone [see Recommendation 8], offer or refer for substance use disorder treatment [see Recommendation 12], all as appropriate).

Recommendation 11

Clinicians should use extreme caution when prescribing opioid pain medication and benzodiazepines concurrently and consider whether benefits outweigh risks of concurrent prescribing of opioids and other central nervous system depressants (recommendation category: B, evidence type: 3).

Implementation Considerations

Although there are circumstances when it might be appropriate to prescribe opioids to a patient who is also prescribed benzodiazepines (e.g., severe acute pain in a patient taking long-term, stable low-dose benzodiazepine therapy), clinicians should use extreme caution when prescribing opioids and benzodiazepines concurrently. In addition, clinicians should consider whether benefits outweigh risks of concurrent use of opioids with other central nervous system depressants (e.g., muscle relaxants, non-benzodiazepine sedative hypnotics, potentially sedating anticonvulsant medications such as gabapentin and pregabalin).

Clinicians should check the PDMP for concurrent controlled medications prescribed by other clinicians (see Recommendation 9) and should consider involving pharmacists as part of the management team when opioids are co-prescribed with other central nervous system depressants.

In patients receiving opioids and benzodiazepines long-term, clinicians should carefully weigh the benefits and risks of continuing therapy with opioids and benzodiazepines and discuss with patients and other members of the patient's care team.

Risks of concurrent opioid and benzodiazepine use are likely to be greater with unpredictable use of either medication, with use of high-dose opioids and high-dose benzodiazepines in combination, or with use with other substances including alcohol (as compared to long-term stable use of low-dose opioids and low-dose benzodiazepines without other substances).

In specific situations, benzodiazepines can be beneficial, and stopping benzodiazepines can be destabilizing.

Buprenorphine or methadone for opioid use disorder should not be withheld from patients taking benzodiazepines or other medications that depress the central nervous system.

If risks are determined to outweigh benefits of continuing opioid and benzodiazepine therapy at current dosages and a decision is made to taper, it might be safer and more practical to taper opioids first. There can be greater risks of benzodiazepine withdrawal relative to opioid withdrawal, and tapering opioids can be associated with anxiety (see Recommendation 5).

Clinicians should taper benzodiazepines gradually prior to discontinuation because abrupt withdrawal can be associated with rebound anxiety, hallucinations, seizures, delirium tremens, and, in rare cases, death. The rate of tapering should be individualized.

If benzodiazepines prescribed for anxiety are tapered or discontinued, or if patients receiving opioids require treatment for anxiety, evidence-based psychotherapies (e.g., CBT) and/or specific antidepressants or other nonbenzodiazepine medications approved for anxiety should be offered.

Clinicians should communicate with clinicians managing the patient to discuss the patient's needs, prioritize patient goals, weigh risks of concurrent benzodiazepine and opioid exposure, and coordinate care. If benzodiazepines prescribed for anxiety are tapered or discontinued, or if patients receiving opioids require treatment for anxiety, evidence-based psychotherapies (e.g., CBT) and/or specific anti-depressants or other nonbenzodiazepine medications approved for anxiety should be offered. Clinicians should communicate with mental health professionals managing the patient to discuss the patient's needs, prioritize patient goals, weigh risks of concurrent benzodiazepine and opioid exposure, and coordinate care.

Recommendation 12

Clinicians should offer or arrange treatment with medication for patients with opioid use disorder (recommendation category: A, evidence type: 1).

Implementation Considerations

Although stigma can reduce the willingness of individuals with opioid use disorder to seek treatment, opioid use disorder is a chronic, treatable disease from which people can recover and continue to lead healthy lives.

If clinicians suspect opioid use disorder, they should discuss their concern with their patient and provide an opportunity for the patient to disclose related concerns or problems.

Clinicians should assess for the presence of opioid use disorder using criteria from the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders*.

For patients meeting criteria for opioid use disorder, particularly if moderate or severe, clinicians should offer or arrange for patients to receive treatment with medication for opioid use disorder.

Clinicians should not dismiss patients from their practice because of opioid use disorder because this can adversely affect patient safety and could represent patient abandonment.

Medication treatment of opioid use disorder has been associated with reduced overdose and overall mortality. Identification of opioid use disorder represents an opportunity for a clinician to initiate potentially life-saving interventions, and it is important for the clinician to collaborate with the patient regarding their safety to increase the likelihood of successful treatment.

For pregnant people with opioid use disorder, medication therapy with buprenorphine or methadone has been associated with improved maternal outcomes and should be offered.

Clinicians unable to provide treatment themselves should arrange for patients with opioid use disorder to receive care from a substance use disorder treatment specialist, such as an office-based buprenorphine or naltrexone treatment provider, or from an opioid treatment program certified by Substance Abuse and Mental Health Services Administration to provide methadone or buprenorphine for patients with opioid use disorder.

All clinicians, and particularly clinicians prescribing opioids in communities without sufficient treatment capacity for opioid use disorder, should obtain a waiver to prescribe buprenorphine.

Clinicians prescribing opioids should identify treatment resources for opioid use disorder in the community and should work together to ensure sufficient treatment capacity for opioid use disorder at the practice level.

Although identification of an opioid use disorder can alter the expected benefits and risks of opioid therapy for pain, patients with co-occurring pain and opioid use disorder require ongoing pain management that maximizes benefits relative to risks.

Management of Opioid Misuse that Does Not Meet Criteria for Opioid Use Disorder

For patients with opioid misuse that does not meet criteria for opioid use disorder (e.g., taking opioids in larger amounts than intended without meeting other criteria for opioid use disorder), clinicians should reassess the patient's pain, ensure that therapies for pain management have been optimized (see Recommendation 2), discuss with patients, and carefully weigh benefits and risks of continuing opioids at the current dosage (see Recommendation 5). For patients who choose to but are unable to taper, clinicians may reassess for opioid use disorder and offer buprenorphine treatment or refer for buprenorphine or methadone treatment if criteria for opioid use disorder are met. Even without a diagnosis of opioid use disorder, transitioning to buprenorphine for pain can also be considered given reduced overdose risk with buprenorphine compared with risk associated with full agonist opioids (see Recommendation 5).

Pain Management for Patients with Opioid Use Disorder

Although identification of an opioid use disorder can alter the expected benefits and risks of opioid therapy for pain, patients with co-occurring pain and substance use disorder require ongoing pain management that maximizes benefits relative to risks. Clinicians should use nonpharmacologic and nonopioid pharmacologic pain treatments as appropriate (see Recommendations 1 and 2) to provide optimal pain management [49]. For patients with pain who have an active opioid use disorder but are not in treatment, clinicians should consider buprenorphine or methadone treatment for opioid use disorder, which can also help with concurrent management of pain [49]. For patients who are treated with buprenorphine for opioid use disorder and experience acute pain, clinicians can consider temporarily increasing the buprenorphine dosing frequency (e.g., to twice a day) to help manage pain, given the duration of effects of buprenorphine is shorter for pain than for suppression of withdrawal [49; 50]. For severe acute pain (e.g., trauma and/or unplanned major surgery), clinicians can consider additional as-needed doses of buprenorphine for patients receiving buprenorphine for opioid use disorder and short-term use of higher-potency nonopioid analgesics (e.g., NSAIDs) for patients receiving naltrexone for opioid use disorder; patients receiving methadone for opioid use disorder who require additional opioids as treatment for pain management should be carefully monitored, and when feasible should optimally be treated by a clinician experienced in the treatment of pain in consultation with their opioid treatment program. [49]. The American Society of Addiction Medicine National Practice Guideline for the Treatment of Opioid Use Disorder (2020 Focused Update) provides additional recommendations for the management of patients receiving medications for opioid use disorder who have planned surgeries for which nonopioid therapies are not anticipated to provide sufficient pain relief [49].

RESPONSE TO THE CDC'S OPIOID PRESCRIBING GUIDELINE UPDATE

It is important to note that the CDC's guidelines are voluntary, and the changes may not result in changes to state laws and rules established to restrict opioid prescribing and help curb opioid misuse following publication of the 2016 guideline. The 2022 draft guideline emphasizes prescriber decision-making and access to necessary opioid analgesics to address unrelenting pain. The guideline states that some policies have extended even beyond the 2016 recommendations, contributing to patient harm, including untreated and undertreated pain, serious withdrawal symptoms, worsening pain outcomes, psychological distress, overdose, and suicidal ideation and behavior [4]. However, state governments seem reluctant to make similar changes, especially as opioid overdose deaths have increased [20].

The American Academy of Pain Medicine, which had expressed dismay with the 2016 CDC guideline and how it was misapplied by insurance companies, state governments, and healthcare organizations, indicated general support for the 2022 revision [21].

IDENTIFICATION OF DRUG DIVERSION/SEEKING BEHAVIORS

Urine drug tests can give insight into patients who are misusing opioids. A random sample of urine drug test results from 800 pain patients 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 [22]. Negative urine drug test 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 urine drug test results and that a negative result for the prescribed opioid or a positive urine drug test may serve as the pretense to terminate a patient rather than guide him/her into addiction treatment or an alternative pain management program [23].

In addition to aberrant urine screens, there are certain behaviors that are suggestive of an emerging opioid use disorder. The most suggestive behaviors are [24; 25; 26]:

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

Behaviors with a lower level of evidence for their association with opioid misuse include [24; 25; 26]:

- 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

interactive activity

View the CDC's video Risk Factors in Opioid Prescribing at https://youtu.be/g9VBbIFurZE. This video addresses the various risk factors likely to increase susceptibility to opioid-associated harms and suggests strategies for mitigating these risks.

FEDERAL AND STATE LAW

In response to the rising incidence in prescription opioid abuse, addiction, diversion, and overdose since the late 1990s, the FDA has mandated opioid-specific REMS to reduce the potential negative patient and societal effects of prescribed opioids. 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 [27].

Several regulations and programs at the state level have been enacted in an effort to reduce prescription opioid abuse, diversion, and overdose, including [28]:

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

CONTROLLED SUBSTANCES LAWS/RULES

The U.S. Drug Enforcement Administration (DEA) is responsible for formulating federal standards for the handling of controlled substances. In 2011, the DEA began requiring every state to implement electronic databases that track prescribing habits, referred to as PDMPs. Specific policies regarding controlled substances are administered at the state level [29].

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 [30]. The abuse rate is a determinate factor in the scheduling of the drug; for example, Schedule I drugs are considered the most dangerous class of drugs with a high potential for abuse and potentially severe psychologic and/or physical dependence.

STATE-SPECIFIC LAWS AND RULES

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

interactive activity

Visit the NetCE website to view excerpts from specific state rules and regulations relating to the regulation of controlled substances, electronic PDMPs, enacted state legislation, and prescribing guidelines.

https://www.netce.com/learning.php?page=activities&courseid=2435.

PATIENT EDUCATION

Patients and caregivers should be counseled regarding the safe use and disposal of opioids. As part of its mandatory Risk Evaluation and Mitigation Strategy (REMS) for extended-release/long-acting opioids, the U.S. Food and Drug Administration (FDA) has developed a patient counseling 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 [11]. A copy of this form may be accessed online at https://www.fda.gov/media/114694/download.

When prescribing opioids, clinicians should provide patients with the following information [11]:

- 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 [31]. According to the FDA, most medications that are no longer necessary or have expired should be removed from their containers, mixed with undesirable substances (e.g., cat litter, used coffee grounds), and put into an impermeable, nondescript container (e.g., disposable container with a lid or a sealed bag) before throwing in the trash [32]. 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 [32; 33]. 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 [33]. Patients should be advised to flush prescription drugs down the toilet only if the label or accompanying patient information specifically instructs doing so.

The American College of Preventive Medicine has established best practices to avoid diversion of unused drugs and educate patients regarding drug disposal [31]:

- 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.

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.

DISPARITIES IN PAIN MANAGEMENT

At greatest risk of unrelieved pain from stigma and bias are children, the elderly, racial and ethnic minorities, active duty or military veterans, and those with cancer, HIV, or sickle cell disease. Pain undertreatment in Black patients is especially widespread, from prevalent misperceptions (often unconscious) that this group has higher pain tolerance and is more likely to abuse their opioid prescription [34]. As a result, prescribers, dispensers, and administrators would benefit from considering both the tenets of appropriate opioid prescribing and the impact of culture on experiences of pain and effective pain management.

It is clear that health disparities exist among racial and ethnic minority groups, and this is true for pain management services and medications. A large-scale national study in the United States found racial differences in the prescription of analgesics for patients with migraine, low back pain, and bone fractures [35]. Specifically, Black Americans were less likely to be prescribed analgesics for their pain compared with their White counterparts. Racial minority patients are also more likely to experience longer wait times for medication compared with White patients [36].

Analysis of a national dataset found that Black Americans were less likely to be prescribed opioids for back pain and abdominal pain compared with non-Hispanic White Americans [37]. The authors speculate that racial biases may influence prescribing behaviors. An examination of Medicaid patients who received epidural analgesia during vaginal childbirth also found statistically significant racial/ethnic differences [38]. In this study, 59.6% of the White patients received epidural analgesia, compared with 49.5% of Black Americans, 48.2% of Asians, and 35.2% of Hispanics. Even after the researchers controlled for age, urban/rural residence, and the availability of anesthesiologists, race and ethnicity still predicted epidural analgesia prescribing trends [38].

In a meta-analysis of ethnicity and pain management researchers found that professionals under-rated ethnic minority patients' levels of pain and were less likely to indicate their pain scores on their charts compared with their White counterparts [39]. In addition, Black American and Hispanic patients were less likely to have been given analgesics than White patients.

Studies have not definitively isolated the factors that contribute to these disparities. One of the challenges in understanding health disparities, and particularly pain management disparities, is the fact that racial and ethnic minority groups are heterogeneous [40; 41]. Healthcare professional barriers may include professionals' beliefs about appropriate pain management; lack of training and knowledge about the intersection of pain and culture, race, and ethnicity; lack of culturally sensitive assessment for pain; and expectations about racial and ethnic minority pain patients based on stereotypes [42]. Consequently, practitioners may underestimate and minimize racial minority patients' pain experiences. In a qualitative study, Native American individuals described their complaints of pain being dismissed, receiving inadequate care, and neglected aftercare [43].

Studies have also shown that the language and race/ethnicity of the healthcare professional influences pain management. For example, the ratings of pain tend to be comparable when the patient and healthcare provider speak the same language. When there is a native language, pain ratings tend to diverge. When literacy and language barriers are eliminated, assessment and treatment improve and racial and ethnic minority patients with pain fare better [44]. In addition, healthcare professionals' level of empathy appears to increase when the patient and healthcare professional share the same skin color or are of the same ethnic group [45; 46].

It is important to note that disparities in pain management are not typically intentional. Instead, they are the result of a myriad of issues, including healthcare system, socioeconomic, and cultural factors. However, prescriber and dispenser unconscious bias can contribute to the undertreatment of pain in certain groups. Promoting positive emotions such as empathy and compassion can help reduce implicit biases. This can involve strategies like perspective taking and role playing [47]. In a study examining analgesic prescription disparities, nurses were shown photos of White or Black American patients exhibiting pain and were asked to recommend how much pain medication was needed; a control group was not shown photos. Those who were shown images of patients in pain displayed no differences in recommended dosage along racial lines; however, those who did not see the images averaged higher recommended dosages for White patients compared with Black patients [48]. This suggests that professionals' level of empathy (enhanced by seeing the patient in pain) affected prescription recommendations.

CONCLUSION

Opioid analgesics are approved by the FDA for the treatment of moderate or severe pain. However, individual patients differ greatly in clinical response to different opioid analgesics, and patient populations show widely variable response to the same opioid and dose. These response variations make opioid prescribing challenging. Further, the important role of opioid analgesics is broadly accepted in acute pain, cancer pain, and palliative and end-of-life care, but it is controversial for the management of chronic noncancer pain. Previous opioid prescribing guidelines have been critiqued for lacking a patient-centered approach and failing to emphasize individualization of therapy. This prompted the 2022 revision of the CDC's opioid prescribing guidelines, the draft of which is outlined in this course.

Opioids are not a panacea for pain, nor are they safe and effective for every patient. However, they can be a useful tool, and knowledge of medical advances can give clinicians greater confidence to safely and effectively prescribe these drugs.

Customer Information/Answer Sheet/Evaluation insert located between pages 96–97.

COURSE TEST - #95500 OPIOID SAFETY: BALANCING BENEFITS AND RISKS

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 5 credit activity must be completed by September 30, 2025.

1. All of the following statements regarding opioid use for chronic pain are TRUE, EXCEPT:
- A) *Opioid therapy for chronic pain should be presented as a trial for a pre-defined period.*
- B) *The goals of treatment should be established with all patients prior to the initiation of opioid therapy.*
- C) *Opioids should not be combined with nonpharmacologic and nonopioid pharmacologic therapy.*
- D) *The treatment plan should describe therapy selection, measures of progress, and other diagnostic evaluations, consultations, referrals, and therapies.*

2. Which of the following is one reason that opioids are useful for severe pain at the end of life?
- A) *Unlike nonopioids, opioids do not have a ceiling effect.*
- B) *Opioid side effects do not occur in patients at the end of life.*
- C) *Nonopioid pharmacotherapy is more difficult to administer to patients.*
- D) *Opioids are generally more acceptable to patients and their families than nonopioid options.*

3. What administration route is typically preferred for opioids at the end of life as it is the most convenient and least expensive?
- A) *Oral*
- B) *Parenteral*
- C) *Transdermal*
- D) *Intramuscular*

4. The 2022 revision of the CDC's guidelines for opioid prescribing apply to which of the following patient groups?
- A) *Hospital inpatients*
- B) *Those with sickle cell disease*
- C) *Persons receiving end-of-life care*
- D) *Adults (18 years of age and older)*

5. The CDC states that which of the following is paramount when treating patients with pain?
- A) *Inclusion of opioids in every chronic pain treatment plan*
- B) *Strict adherence to established opioid prescribing guidelines*
- C) *Flexibility to meet the care needs and the clinical circumstances of a specific patient*
- D) *Implementing policies that limit opioid access regardless of pain severity, quality, or effectiveness of nonopioid therapy*

6. The CDC recommends which of the following noninvasive, nonpharmacologic approaches for the treatment of subacute or chronic neck pain?
- A) *Exercise therapy*
- B) *Mind-body practices*
- C) *Low-level laser therapy*
- D) *Cognitive-behavioral therapy*

7. In which case might opioid therapy be discontinued abruptly?
- A) *Pregnancy*
- B) *Constipation*
- C) *Signs of impending overdose*
- D) *Desire to discontinue therapy*

8. Following initiation of opioid therapy for subacute or chronic pain or dose escalation, clinicians should evaluate benefits and risks with patients
- A) *within one to four weeks.*
- B) *after one month.*
- C) *every three months.*
- D) *annually.*

Test questions continue on next page ➔

9. Clinicians should offer naloxone when prescribing opioids to patients at increased risk for overdose. Which of the following patients would be considered at increased risk for overdose?

A) A patient older than 65 years of age
B) A patient with obstructive sleep apnea
C) A patient taking lower dosages of opioids
D) A patient who is also taking an antidepressant

10. Which of the following statements regarding toxicology testing is NOT in accordance with CDC guidance?

A) Clinicians should dismiss patients from care based on a toxicology test result.
B) Clinicians should use unexpected toxicology test results to improve patient safety.
D) Clinicians who believe their patient might be diverting prescription opioids should consider toxicology testing to assist in determining whether prescription opioids can be discontinued without causing withdrawal.
C) When prescribing opioids for subacute or chronic pain, clinicians should consider toxicology testing to assess for prescribed medications as well as other prescribed and non-prescribed controlled substances.

11. For pregnant people with opioid use disorder, which pharmacotherapy is recommended?

A) Fentanyl
B) Bupropion
C) Naltrexone
D) Buprenorphine or methadone

12. 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

13. 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

14. All of the following should be included in the education of patients prescribed opioids, EXCEPT:

A) Product-specific information
B) Risk factors, signs, and symptoms of overdose
C) Instructions for safe sharing of opioids with others
D) Warning and rationale to avoid other central nervous system depressants

15. Implicit biases can impact opioid prescribing practices. Which of the following strategies can promote positive emotions and help reduce implicit biases?

A) The use of interpreters
B) Frequent career changes
C) Perspective taking and role playing
D) Increased opioid prescribing for racial/ethnic minority patients

Be sure to transfer your answers to the Answer Sheet insert located between pages 96–97.
PLEASE NOTE: Your postmark or facsimile date will be used as your test completion date.

Sleep Disorders

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 ABA MOC Points, 10 ABP Points, 10 ABO MOC Points.

Audience
This course is designed for all healthcare professionals, including physicians, nurses, pharmacists, and mental health practitioners, who are involved in the care of patients experiencing a sleep-related disorder.

Course Objective
Many of the complications associated with sleep disorders are preventable, making early diagnosis and appropriate treatment vital. The purpose of this course is to provide healthcare professionals with the information necessary to identify and effectively treat sleep disorders, thereby improving patients' quality of life and preventing possible complications.

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

1. Discuss the physiology of normal sleep.
2. Describe the classification of sleep disorders.
3. Compare and contrast the types of insomnias and their associated diagnosis and treatment.
4. Evaluate the major types of sleep-related breathing disorders, particularly obstructive sleep apnea.
5. Identify the clinical signs and symptoms of narcolepsy.
6. Outline the characteristics of non-narcolepsy hypersomnias.
7. Analyze the complications and symptoms of circadian rhythm sleep disorders.
8. Describe the characteristics, diagnosis, and treatment of parasomnias.
9. Evaluate the presentation and treatment of sleep-related movement disorders.
10. Assess considerations for patients with sleep disorder who have low English literacy.

Faculty
Teisha Phillips, RN, BSN, received her Bachelor of Science in Nursing degree from Point Loma Nazarene University in 2005. She has nursing experience in a variety of clinical settings including multispecialty outpatient surgery, fertility, women's health, and cosmetic/aesthetic nursing. Her primary focus and passion is on direct patient care and patient education. She is presently employed as a perioperative nurse at an outpatient surgery center in the greater Sacramento area.

Faculty Disclosure
Contributing faculty, Teisha Phillips, RN, BSN, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Division Planner
John M. Leonard, MD

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
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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.

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®.

This activity has been approved for the American Board of Anesthesiology's® (ABA) requirements for lifelong learning and self-assessment. This activity contributes 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. 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 10 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.

Successful completion of this CME activity, which includes participation in the evaluation component, earns credit toward the Lifelong Learning requirement(s) for the American Board of Ophthalmology's Continuing Certification program. It is the CME activity provider's responsibility to submit learner completion information to ACCME for the purpose of granting 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.

Special Approvals

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

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.

Our contributing faculty members have taken care to ensure that the information and recommendations are accurate and compatible with the standards generally accepted at the time of publication. The publisher disclaims any liability, loss or damage incurred as a consequence, directly or indirectly, of the use and application of any of the contents. Participants are cautioned about the potential risk of using limited knowledge when integrating new techniques into practice.

Disclosure Statement

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- Read the following course.
- Complete the test questions at the end of the course.
- Return your Customer Information/Answer Sheet/Evaluation, and payment to NetCE by mail or fax, or complete online at **www.NetCE.com/MD23**.
- 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

Sleep is one of the most vital processes of life and serves many important functions, including preservation, restoration, and memory processing. Repeated disruption of the natural sleep cycle or failure to initiate sleep (i.e., sleep disorder) can lead to a sleep deficit, which in turn causes physical, mental, and emotional fatigue. Most individuals with a sleep disorder experience a myriad of symptoms and a reduction in quality of life [1].

The American Academy of Sleep Medicine (AASM) publication *The International Classification of Sleep Disorders, Third Edition* (ICSD-3) identifies more than 80 official sleep disorders [2]. Many are uncommon, but a handful (e.g., insomnias, obstructive sleep apnea, narcolepsy, restless legs syndrome) affect millions of Americans and are responsible for significant morbidity and mortality, including direct physiologic and/or psychologic complications and accidents associated with moderate or severe drowsiness.

It is estimated that 50 to 70 million adult Americans have a sleep or wakefulness disorder [1]. Some of the most serious long-term health consequences of sleep disorders (or sleep insufficiency/deficit) include glucose intolerance, increased blood pressure, increased inflammatory markers, higher evening cortisol levels, weight gain/obesity, and an increased risk of myocardial infarction, depression, and cancer [1; 3; 4]. Additionally, the National Highway Traffic Safety Administration (NHTSA) estimates that in 2017, 91,000 police-reported crashes involved drowsy drivers. These crashes led to an estimated 50,000 people injured and nearly 800 deaths. In 2019, there were 697 deaths from drowsy-driving-related crashes [5].

The economic cost of sleep disorders should not be underestimated. One study found that individual healthcare costs were approximately doubled for patients with undiagnosed obstructive sleep apnea [6]. Research commissioned by Congress in 1993 found that direct annual medical costs for insomnia were $15.2 billion (with the amount spent on over-the-counter products not included), and that the indirect and related annual costs (mostly costs arising from accidents) approached $56 billion [4; 7; 8; 9]. In 2020, the aggregate total of direct and indirect insomnia healthcare costs has been estimated to be as high as $100 billion U.S. dollars per year [10].

A 2011 study found that annual workplace losses (including workplace accidents) due to insomnia and associated comorbidities totaled $91.7 billion per year [11]. The study, using extrapolated data from 7,428 U.S. workers enrolled in healthcare plans, found that presenteeism (i.e., attending work while drowsy) accounted for the majority of the losses (roughly two-thirds) and absenteeism accounted for the remainder. Comorbidity is a major factor, yet after 26 conditions were controlled for, the net annual costs of insomnia alone were $63.2 billion [11]. One limitation of the study was that only data from workers with healthcare insurance were sampled. Although the prevalence of insomnia may be similar among insured and uninsured populations, undiagnosed and untreated sleep disorders can amount to greater overall long-term cost. A 2015 study reiterated the negative impact on work performance (e.g., absenteeism, presenteeism, workplace injury, accidents driving to/from work) of one sleep disorder in particular, obstructive sleep apnea [12].

Sleep disorders have a clear impact on productivity and public health. The AASM and the Institute of Medicine emphasize that education on somnology and sleep medicine should be incorporated into continuing education programs [1]. Many of the complications associated with sleep disorders are preventable, making early diagnosis and appropriate treatment vital. Unfortunately, research indicates that sleep disorders continue to be underdiagnosed and undertreated [13; 14; 15; 16]. One study of relatively healthy patients seeking preventive care found that 57% either reported a sleep complaint related to sleep apnea or were found to be at increased risk for the condition [14]. However, only 11% of individuals who reported sleep complaints underwent any subsequent diagnostic testing, indicating a gap in factual knowledge and appropriate clinical behaviors [14].Outbreaks of infectious diseases, such as the 2019 novel coronavirus (2019-nCoV/SARS-CoV-2 [COVID-19]), also are associated with major psychologic distress and significant symptoms, including poor sleep quality [17; 18]. A systematic review and meta-analysis, conducted to examine the impact of the pandemic on the prevalence of sleep problems among the general population, healthcare workers, or patients with COVID-19, found a prevalence of approximately 40% among the general and healthcare populations, with a higher prevalence of sleep problems among patients with active COVID-19 [19]. The review included a total of 44 studies published after March 2020 that involved 54,231 participants from 13 countries.

This course will provide information regarding the physiology of sleep; the causes, risk factors, epidemiology, and pathophysiology of various sleep disorders; diagnosis, including patient history, assessment of sleep habits, physical examination, laboratory tests, and sleep studies; and treatments to improve sleep patterns, including lifestyle/behavioral change (e.g., "sleep hygiene"), pharmacologic interventions, surgical interventions, and other treatment options for patients.

THE PHYSIOLOGY OF SLEEP

Sleep is an active body process marked by suspended consciousness, diminished sensory activity, relaxed musculature, reduced ability to react to stimuli, and other changes in brain activity that correspond with distinct sleep phases. Despite being necessary to humans, the basis for the need of sleep is still poorly understood. To date, the consequences of sleep deficit are the best indication of the functions sleep serves.

CIRCADIAN RHYTHMS, HOMEOSTASIS, AND THE SLEEP-WAKE CYCLE

The sleep-wake cycle consists of approximately 8 hours of sleep and 16 hours of wakefulness in healthy adults and is controlled by two internal factors: circadian rhythms and sleep homeostasis [20]. Circadian rhythms are "physical, mental, and behavioral changes that follow a roughly 24-hour cycle, responding primarily to light and darkness in an organism's environment" [21]. Biologic "clocks" located throughout the body manage circadian rhythms in individual body systems; these are all controlled and coordinated by the suprachiasmatic nucleus (SCN), or "master clock," located in the hypothalamus. The SCN's circadian rhythm has an endogenous component but is also driven by external cues from the environment, called zeitgebers [22]. The light-dark cycle is the overwhelmingly dominant zeitgeber for humans. Light acts on photosensitive ganglion cells in the retina that send signals directly to the SCN, providing synchronization with the particular environment. Thus, the body is able to adapt (in some cases with difficulty) and correct the sleep-wake cycle relative to differing light-dark conditions (e.g., when travelling to a different time zone).

Endogenous circadian rhythms, and therefore sleep needs, vary among individuals and age groups. Adolescents typically need 9.5 hours of sleep, and infants require 16 hours of sleep [23]. There are three chronotypes (identifiable using the Horne-Östberg questionnaire): morning type, an early circadian phase; evening type, a late circadian phase; and intermediate type. This is important because morning-type individuals typically sleep earlier and longer and are quicker to adjust to changes in sleep schedules than intermediate and evening types [23; 24]. One study found that morning-type individuals are also less likely to deviate from their normal sleep schedule regardless of social cues (e.g., being on vacation) [23]. A 2012 study found that adolescents living in brightly lit, urban environs had a "stronger evening-type orientation than adolescents living in darker and more rural municipalities" [25]. The study also found that nighttime electronic-screen media use (i.e., a strong artificial light source) correlated with an evening-type rhythm in adolescents living in darker areas, but a morning rhythm could be established if limited and appropriate nighttime lighting (e.g., dimmer room lights, heavy curtains to block street lighting, no electronic-screen media use) was used.

Although the primary zeitgeber in humans is the light-dark cycle, there are other influential nonphotic cues, including exercise, temperature, and various social cues, that influence the regulation of various biologic processes (e.g., body temperature, hormone production) [23; 26; 27]. Researchers propose that sleep patterns may be influenced by other important zeitgebers, including sound, temperature, and the earth's magnetic field, that are as yet unproven or only considered weak factors [28; 29]. Given that light is such a powerful influence and that humans are sensitive to very low levels of light, it is difficult to study the effects of these other possible cues. (Blind individuals typically have "free running" circadian rhythms ≥25 hours and are often the subject of zeitgeber investigations.) Some zeitgebers, such as aberrant work schedules, alarm clocks, artificial light, radio, television, and time-zone change, are known to cause disruptions to the natural sleep-wake cycle.

Homeostasis is the body process associated with maintaining a steady state of internal conditions (e.g., acid-base balance, blood pressure, body temperature). The sleep drive and amount of sleep are also under homeostatic control [30]. The neurochemistry of sleep is not fully understood, but the neurotransmitter adenosine is thought to have an important role as a homeostatic regulator of sleep [30; 31]. Adenosine does not act as a classical neurotransmitter; it is neither stored nor released, but is instead thought to be formed inside or on the surface of cells [30; 31]. The drive for sleep (and, alternately, wakefulness) has been found to be directly related to extracellular adenosine levels in the cerebral cortex and basal forebrain [31]. Concentrations of the chemical increase throughout the day and decrease during the sleep recovery period, and the feeling of intense sleepiness following prolonged wakefulness is thought to be caused by very high adenosine levels. Adenosine is a theoretical link between the humoral and neural mechanisms of sleep-wake regulation [31].

Produced in the pineal gland, melatonin is another key sleep hormone. It is regulated by darkness signals from the SCN and also provides feedback to that circadian oscillator [32; 33]. Circulating melatonin levels increase in the hours following nightfall and drop significantly upon eye exposure to light. It is believed that this hormone supplements and reinforces the entraining effects of the light period [32]. Whereas the ganglion cells provide a light cue to the SCN, melatonin provides a darkness cue via receptors in and around the structure [33].

SLEEP STAGES

The sleep process consists of four stages of sleep, divided into two general categories: rapid eye movement (REM) sleep and non-REM sleep (NREM). These stages are divided into five phases: wake, N1, N2, N3, and R [34]. While both alpha and beta waves are present during open-eye wakefulness, beta predominates. As drowsiness increases and the eyes close, the alpha rhythm becomes predominant [34].

NREM sleep consists of three distinct stages (N1, N2, N3), each of which is defined by a set of unique electrophysiologic parameters, including electroencephalogram (EEG), electromyogram (EMG), eye movements, and respiration [34]. When awake, EEG measurements of brainwave activity show frequencies of 8 Hz or greater. When a patient is awake but relaxed with eyes closed, EEG measurements fall in the alpha range (8 to 12 Hz) when measured at posterior head regions. In children, this basic rhythm is in the theta range (4 to 8 Hz), and in infants, it is in the delta range (slower than 4 Hz). A return to wakeful levels of brain activity (greater

than 12 Hz) occurs if the subject opens his or her eyes or engages in mental activity. When awake or when relaxing with eyes closed, muscle tone is normal and individuals are fully aware of their surroundings.

N1 (Stage 1)

During stage 1 sleep, individuals begin to feel drowsy but can be easily aroused. Relaxation of musculature begins, as does reduced environmental awareness [20]. Slow and rolling lateral eye movements also may occur. EEG brain activity shows interruption of the posterior dominant rhythm (i.e., alpha dropout) and the onset of a low-voltage, intermixed pattern of frequencies [35; 36]. Positive occipital sharp transients of sleep (POSTS) and very brief vertex sharp waves may occur in repetitive runs. (POSTS start around 4 years of age, are common by 15 years of age, and decline after 50 years of age.) Hypnagogic hypersynchrony, or bursts of high-amplitude, diffuse, rhythmic (sinusoidal) delta activity, can arise, especially among children 3 months to 13 years of age and is considered a normal variant of drowsiness in this age group. This stage tends to last one to five minutes, consisting of around 5% of the total cycle [34].

N2 (Stage 2)

Approximately 50% of time is spent in stage 2 sleep during an adult's normal night's sleep [20; 34]. Arousal is more difficult during this phase, and the low-voltage, intermixed pattern continues. Brainwave activity slows to the theta range (4 Hz to 7 Hz). Sleep spindles (and associated K-complexes) are the defining characteristic of stage 2 sleep. Spindles are short bursts of vertex rhythmic activity between 12 and 16 Hz (typically 14 Hz) lasting about 0.5 seconds. Sleep spindles begin at 6 to 8 weeks of age and continue throughout life [34; 35; 36].

N3 (Stage 3)

This is considered the deepest stage of sleep [34]. Muscle tone continues to decrease progressively through stage 3. Arousal is most difficult during these stages, which are marked by slow-wave sleep consisting of progressively increasing high-voltage, delta-range brain activity. During stage 3, delta activity comprises as much as 50% or more of brainwave activity [35; 36]. Sleep spindles may still occur in these stages but are not a major feature. Over a lifetime, the amount of time spent in slow-wave sleep decreases [20]. Cognitive testing shows that individuals awakened during this stage tend to have mental performance that is moderately impaired for 30 minutes to 1 hour [34]. During N3, the body repairs and regrows tissues, builds bone and muscle, and strengthens the immune system [34].

REM Sleep

As the name suggests, the major feature of REM sleep is rapid eye movement, but this stage is also characterized by muscle atonia and EEG desynchronization [20]. Brainwave activity returns to a low-voltage intermixed pattern and becomes faster (beta and theta range), almost resembling wakefulness. Dreaming is most likely to occur in this stage. Central activity in the theta range can produce waves with a "saw tooth" appearance on a polysomnogram display.

In healthy adults, about four or five sleep cycles, each about 90 minutes, occur in one night, each one progressing through the non-REM stages, followed by REM sleep [20]. Slow-wave sleep is lessened and REM sleep becomes more predominant with each successive sleep cycle [37].

Some individuals enter REM sleep before descending through non-REM phases, which is referred to as sleep-onset REM periods (SOREMPs). This is considered an indicator of a sleep disorder, usually narcolepsy, but it may also occur in patients with obstructive sleep apnea [33; 38]. SOREMPs are uncommon in the healthy adult population but are slightly more prevalent in individuals with excessive sleepiness (e.g., adolescents and young adults, shift workers) [39]. SOREMPs are also seen with other disorders, including Prader-Willi syndrome, Kleine-Levin syndrome, Parkinson disease, and periodic limb movement disorder (PLMD) [40].

OVERVIEW OF SLEEP DISORDERS

As discussed, there are more than 80 official sleep disorders defined in the current AASM diagnostic and coding manual, the ICSD-3 [2]. The ICSD-3 uses a pragmatic framework for categorizing sleep disorders based primarily on pathophysiology, if known, and also phenomenology and organ system methodology [2]. Unlike in original versions, disorders are no longer grouped into three major classes: dyssomnias, parasomnias, and sleep disturbances associated with mental, neurologic, or other medical disorders. Instead, the ICSD-3 contains seven major categories of sleep disorders [2]:

- Insomnia
- Sleep-related breathing disorders
- Central disorders of hypersomnolence
- Circadian rhythm sleep-wake disorders
- Parasomnias
- Sleep-related movement disorders
- Other sleep disorders

A goal of the ICSD-3 framework was to organize sleep disorders into an International Classification of Diseases (ICD-10)-compatible format [2]. Another goal was to describe in detail all currently recognized sleep and arousal disorders, which is a missing feature of other manuals, including the widely used *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), while still maintaining a good degree of concordance with the DSM-5.

DSM-5 CLASSIFICATION

The DSM-5 contains information for making a diagnosis of a sleep disorder; however, it has less detailed descriptions of certain sleep-wake disorders than the ICSD-3. For example, the DSM-5 section on insomnia disorders does not extensively describe each of the three forms of insomnia described in the ICSD-3. The DSM-5 takes what it refers to as a "lumping versus splitting" approach to classifying sleep-wake disorders. The insomnias identified in the ICSD-3 fall under the general category of insomnia disorder in the DSM-5, lumped together due to their similar presentations and impact on clinical care for nonspecialists. While this course incorporates information from both the DSM-5 and the ICSD-3, the organization structure of the latter will be used as an outline. The following sections will discuss the more common examples of each of the seven categories, and those with the greatest incidence will be discussed in more detail.

SLEEP STUDY TESTS

Many tests are available to assess the quality of an individual's sleep, and a discussion of each is beyond the scope of this course. However, the most commonly used tests are polysomnography and the multiple sleep latency test (MSLT), both of which are used in the evaluation of many sleep disorders.

Polysomnography is preferably conducted by a certified sleep technologist at an AASM-accredited facility. This test monitors many physiologic parameters, including electrocardiogram, EEG, eye movements (electrooculogram), chin EMG, airflow, oxygen saturation, respiratory effort, and heart rate [41]. A technician will note if snoring is present and, if so, the degree (i.e., mild, moderate, or severe). Body position and leg EMG derivations are also recommended.

One full-night study is typical, but split-night studies (i.e., polysomnography followed by continuous positive airway pressure [CPAP] titration) may be used when initial monitoring shows a high apnea-hypopnea index (AHI) score. This index will be discussed in detail later in this course. The *AASM Manual for the Scoring of Sleep and Associated Events* is used to set up and analyze the study, and the results are reported as an AHI score (or a respiratory disturbance index) for review by a qualified sleep physician. Polysomnography can help rule out the possibility of sleep disorders, and it will also show if the patient's sleep cycle is normal or if REM sleep occurs at unusual times.

Portable monitor testing has a known likelihood of producing false-negative results; therefore, it is considered inferior to overnight sleep lab polysomnography [41]. Airflow, blood oxygenation, and respiratory effort are the minimum test parameters needed for a complete at-home study. The sensors are similar or identical to those used for polysomnography and will either be placed by a sleep technologist, other trained professional, or the patient following detailed instruction. The AHI score is calculated per the *AASM Manual* using the truncated portable monitor test data. Tests of patients who have a high probability of obstructive sleep apnea and a low AHI should be considered inaccurate and should be repeated (in a sleep lab whenever possible) [41].

The MSLT is a daytime test that can determine if REM sleep patterns occur during wakefulness and monitor the amount of time it takes for the patient to fall asleep normally during the day. For example, sleep latency periods (i.e., the time it takes to fall asleep) are typically 8 minutes or less in narcoleptic patients, but healthy individuals usually take 12 or more minutes to fall asleep during the daytime [42].

INSOMNIAS

The term insomnia is defined generally as difficulty with initiation, duration, consolidation, or quality of sleep. It is commonly applied when three conditions are satisfied: ample time and opportunity for sleep, persistent sleep difficulty, and daytime dysfunction associated with sleep deficit [2].

Chronic or short-term insomnia is a problem for most people at some point in their lives. Patients will experience problems going to sleep or staying asleep and are distressed by the number of hours they are awake at night or by a quality of sleep perceived as poor [2]. However, if daytime function is unaffected, the complaint does not warrant treatment other than discussion and education, because by definition they do not have an insomnia disorder. Patients with clinically significant insomnia typically become fatigued, irritable, cognitively impaired, and/or depressed and some complain of headaches, muscle tension, palpitations, work impairment, and social withdrawal [2].

There are now three formal insomnia diagnoses listed in the ICSD-3: chronic insomnia disorder, short-term insomnia disorder, and other insomnia disorder [2]. This is a significant departure from the previous version of the ICSD, which included 11 diagnoses. Many sleep disorders diagnosed in the past have a complaint of insomnia in common. These included adjustment insomnia (acute insomnia); psychophysiologic insomnia; paradoxical insomnia; idiopathic insomnia; insomnia due to mental disorder; inadequate sleep hygiene; behavioral insomnia of childhood; insomnia due to drug or substance; insomnia due to medical condition; insomnia not due to a substance or known physiologic condition, unspecified (nonorganic insomnia, not otherwise specified [NOS]); physiologic (organic) insomnia, unspecified (organic insomnia, NOS).

Insomnia is no longer regarded as either being due only to a primary sleep disorder or because of an underlying medical or psychiatric condition (i.e., as a primary disorder or as a disorder secondary to another comorbid condition). For one, the symptoms and features of primary and secondary insomnia overlap considerably, and differentiation was often difficult or impossible. Additionally, patients usually met the criteria for more than one ICSD-2 insomnia subtype. Evidence has

CLINICAL AND PATHOPHYSIOLOGIC SUBTYPES IN THE ICSD-3		
Diagnosis	**Features**	**Symptoms**
Psychophysiologic insomnia	Elevated levels of somatic and cognitive arousal, especially when trying to sleep Learned sleep-preventing associations Excessive focus on sleep Excessive worry about sleep	Difficulty sleeping in usual sleep setting (e.g., at home), but may fall asleep easily away from home or at home when not trying to sleep
Idiopathic insomnia	Early onset (i.e., infancy) Genetic or congenital alterations in sleep-induction/arousal systems in the brain No genetic markers are known	Gradual inability to sleep beginning at a very young age with no discernible cause
Paradoxical insomnia	Individuals underestimate the amount of sleep actually obtained Complaint of wakefulness in spite of sleep studies showing normal amounts of sleep Altered sleep/wake system	Extreme subjective sleep disturbance without objective corroboration
Inadequate sleep hygiene	Frequent napping/irregular sleep schedule Regular use of caffeine, alcohol, tobacco, or other drugs close to bedtime Regularly engaging in mentally, physically, or emotionally stressful activity before bedtime Using the bed for activities other than sleep or sex (e.g., reading, television, video games) Inappropriate pre-sleep and sleep environment (e.g., too hot, excessive light, too loud or quiet)	Inability to initiate sleep Chronic sleep/wake difficulty
Behavioral insomnia of childhood (sleep-onset association type or limit-setting type)	Poor sleep training or limit setting by caretakers or parents Some children are a mixed type	Child's dependence on specific objects, settings, or stimulation for initiating or returning to sleep (sleep-onset association type) Bedtime stalling or refusal (limit-setting type)
Source: [2]		*Table 1*

shown that when a patient's underlying medical condition causing insomnia is treated, the insomnia often persists, or when the insomnia was treated, both the comorbid medical condition and the sleep disorder improved [2]. The first two categories of insomnia—chronic insomnia disorder and short-term insomnia disorder—now reflect an all-encompassing view of disordered sleep and are based on various levels of sleep dysfunction. The third category — other insomnia—is included in the ICSD-3 to describe individuals with difficulty initiating and maintaining sleep, but who do not meet the criteria for the other two categories. The AASM does not foresee many individuals receiving this diagnosis, and it will not be discussed in this course.

CHRONIC INSOMNIA DISORDER

According to the ICSD-3, chronic insomnia disorder is defined as "chronic sleep onset and/or sleep maintenance complaints with associated daytime impairment, and is reserved for individuals whose sleep difficulties exceed minimal frequency and duration thresholds shown to be associated with clinically significant morbidity outcomes" [2]. This diagnosis encompasses many insomnia subtypes found in other texts, including primary insomnia, comorbid insomnia, chronic insomnia, secondary insomnia, sleep-onset association disorder, behavioral insomnia of childhood, disorder of initiating and maintaining sleep, and limit-setting sleep disorder. As discussed, this consolidation is not for the sake

of simplicity, but reflects the actual state of current knowledge and evidence regarding chronic insomnia. The specific primary insomnia clinical/pathologic subtypes that are now considered part of this larger, global class in the ICSD-3 are shown in ***Table 1*** [2].

Although these subtypes are discussed in the ICSD-3, a diagnosis of chronic insomnia disorder should be made for all adult and pediatric patients who have a complaint of persistent and frequent insomnia, despite the absence or presence of a comorbid medical disorder, psychiatric disorder, or substance abuse [2]. Given the state of knowledge and evidence regarding insomnia, this has been deemed the most justifiable approach and is more compatible with the DSM-5.

Epidemiology

Approximately 10% of the adult population is affected by chronic insomnia disorder as defined by the ICSD-3 [2]. The disorder is more common in women than in men and affects a greater number of individuals with low socioeconomic status versus those who are economically and socially stable. Patients with medical, psychiatric, and/or substance abuse problems are disproportionately affected. Older individuals are more often diagnosed with chronic insomnia, likely due to medical conditions, medications used to treat them, and age-related sleep continuity decline [2]. Transient insomnia affects 30% to 35% of the adult population.

Prevalence of insomnia in children and adolescents is estimated at 10% to 30% and 3% to 12%, respectively, with wide variance due to definitions of insomnia used in research. It is more frequently diagnosed in adolescent girls than boys [2]. Although the specific ICSD-3 diagnosis has changed, the problems associated with childhood sleep disorders have not. Most chronic childhood insomnia cases are due to caregiver/parental behavior, bedtime interactions, and cultural influences, and the underlying difficulties are still primarily sleep-onset and/or limit-setting problems [2]. The need for and provision of nighttime contact varies among cultures, which should be taken into account. Infants do not establish a regular sleep pattern until approximately 3 to 6 months of age, and an insomnia diagnosis is typically not made before 6 months of age.

The evidence for familial occurrence of insomnia is weak, but there does appear to be some influence, particularly between mothers and daughters, monozygotic twins, and, to some extent, other first-degree relatives [2]. It is not known what the association(s) may be; theories range from learned behavior and a shared environment to genetic predisposition and the byproduct of a common psychopathology.

Diagnosis in Adults

A diagnosis of chronic insomnia disorder is based primarily on subjective reports from adult patients and objective and subjective reports for children and adolescents. The differential diagnosis of chronic insomnia may include a sleep study, if warranted, but typically is not needed for routine evaluation.

There are three features of chronic insomnia disorder [2]. The first is frequent and persistent difficulty initiating or maintaining sleep, and this is the intrinsic essential feature of chronic insomnia disorder [2]. This repetitive failure results in the patient's general dissatisfaction with sleep and quality of life. Insomnia, though chronic, does not necessarily occur every night. Some patients will have episodes of recurrent insomnia, while others constantly struggle with sleep insufficiency. It is common for individuals with persistent insomnia to have several bad nights of sleep with an occasional good sleep [2]. Other patients who are predisposed to insomnia may experience poor sleep in relation to stressful life events. An initial episode of acute insomnia related to a stressful event will typically resolve in most individuals as they adjust to their new reality; however, this episode has the potential to become a chronic problem for some patients. The remembrance and anticipation of insomnia following a stressful event, coupled with actual sleep difficulties and daytime impairment, can lead to a cycle of disordered sleep [2].

The second feature of chronic insomnia is worry about sleep difficulties and/or academic, family, social, vocational, or other functional impairment [2]. Patients with insomnia often display excessive preoccupation with sleep, which can be problematic. Worrying about not getting enough sleep and not being able to initiate sleep following an episode of insomnia can lead to a vicious cycle of becoming tense or agitated as bedtime approaches (with corresponding adrenaline release), trying too hard to sleep (e.g., lying in bed for extended periods of time), becoming increasingly distressed and agitated at the inability to sleep, and being further unable to initiate sleep [43].

Preoccupation with general health and wellness may predispose individuals to chronic insomnia, and repression and internalization of disturbing feelings may be a common trait [2]. It may appear that patients are overly anxious, and in fact, recurrent thoughts of poor sleep performance may trouble these individuals in the morning and afternoon and attain a peak at night. However, generalized anxiety is not the norm for chronic insomnia sufferers. Screening for comorbid general anxiety is recommended when symptoms seem to extend beyond an emphasis on disordered sleep [2]. Environmental and biologic sleep cues often become triggers for heightened sleep anxiety and arousal. For example, when the sun sets and darkness falls, thoughts of poor previous nights' sleep and sleep performance anxiety may begin. In healthy individuals, feelings of drowsiness lead to increased calm, but fatigue can cause panic and distress in those with chronic insomnia. Patients may think, "I feel tired, but I know that if I go to bed I will not be able to fall asleep," or, "I feel tired now, but I am going to feel even worse tomorrow morning when I am not able to sleep tonight." This may be, or become, true as the patient ruminates about sleep and stresses.

THE ICSD-3 DIAGNOSTIC CRITERIA FOR CHRONIC INSOMNIA DISORDER

A. The patient reports, or the patient's parent or caregiver observes, one or more of the following[a]:
   1. Difficulty initiating sleep
   2. Difficulty maintaining sleep
   3. Waking up earlier than desired
   4. Resistance to going to bed on appropriate schedule
   5. Difficulty sleeping without parent or caregiver intervention

B. The patient reports, or the patient's parent or caregiver observes, one or more of the following related to the nighttime sleep difficulty:
   1. Fatigue/malaise
   2. Attention, concentration, or memory impairment
   3. Impaired social, family, occupational, or academic performance
   4. Mood disturbance/irritability
   5. Daytime sleepiness
   6. Behavioral problems (e.g., hyperactivity, impulsivity, aggression)
   7. Reduced motivation/energy/initiative
   8. Proneness for errors/accidents
   9. Concerns about or dissatisfaction with sleep

C. The reported sleep/wake complaints cannot be explained purely by inadequate opportunity (e.g., enough time is allotted for sleep) or inadequate circumstances (e.g., the environment is safe, dark, quiet, and comfortable) for sleep.

D. The sleep disturbance and associated daytime symptoms occur at least three times per week.

E. The sleep disturbance and associated daytime symptoms have been present for at least three months.[b]

F. The sleep/wake difficulty is not better explained by another sleep disorder.

[a]Reports of difficulties initiating sleep, difficulties maintaining sleep, or waking up too early can be seen in all age groups. Resistance to going to bed on an appropriate schedule and difficulty sleeping without parent or caregiver intervention is seen most commonly in children and older adults who require the supervision of a caretaker due to a significant level of functional impairment (e.g., those with dementia).

[b]Some patients with chronic insomnia may show recurrent episodes of sleep/wake difficulties lasting several weeks at a time over several years, yet not meet the three-month duration criterion for any single such episode. Nonetheless, these patients should be assigned a diagnosis of chronic insomnia disorder, given the persistence of their intermittent sleep difficulties over time.

Source: Reprinted with permission from American Academy of Sleep Medicine. The International Classification of Sleep Disorders-3: Diagnostic and Coding Manual. 3rd ed. Westchester, IL: American Academy of Sleep Medicine; 2014. *Table 2*

Subjective or objective deficits with daily functioning are noticed in individuals with chronic insomnia. These may manifest as depression, lethargy, or a desire to limit activities or work. Work productivity may suffer, as may academic performance.

Patients often readily express sleep anxiety and may acknowledge their ability to sleep normally in unfamiliar settings [2]. The lack of environmental triggers in unfamiliar environments can help prevent sleep performance worry.

The third essential feature of chronic insomnia disorder is inability to sleep and remain asleep despite plenty of time to sleep, no nighttime interruptions, an adequate sleep environment, and other sufficient circumstances [2]. Practicing sleep hygiene, or maintaining an ideal sleep environment and optimum mental/physical state to promote sleep, is discussed later in this course.

Diagnosis in Children

The diagnosis of chronic insomnia in children is somewhat different because of the strong influence of parental/caregiver and environmental factors on development. Parents should be questioned regarding their expectations for their child's sleep. Putting children to bed prematurely or allocating too much time in bed can cause sleep difficulties that may lead to chronic insomnia [2]. On the other hand, parents may not be implementing or enforcing regular bedtimes or may allow children to postpone bedtimes. As children develop greater language skills and seek individuality, limit setting becomes more important. Studies have also shown that parents of children who faced a life-threatening illness are less strict about enforcing bedtimes and allow their children greater leeway with sleeping (e.g., joining the adult bed upon waking) [2]. Abuse and unstable home environments are also known factors for insomnia in children and adults. Crowded

THE EPWORTH SLEEPINESS SCALE	
Situation	**Score**[a]
Sitting and reading	0 = No chance of dozing 1 = Slight chance of dozing 2 = Moderate chance of dozing 3 = High chance of dozing
Watching television	0 = No chance of dozing 1 = Slight chance of dozing 2 = Moderate chance of dozing 3 = High chance of dozing
Sitting inactive in a public place (e.g., a theater or a meeting)	0 = No chance of dozing 1 = Slight chance of dozing 2 = Moderate chance of dozing 3 = High chance of dozing
As a passenger in a car for an hour without a break	0 = No chance of dozing 1 = Slight chance of dozing 2 = Moderate chance of dozing 3 = High chance of dozing
Lying down to rest in the afternoon when circumstances permit	0 = No chance of dozing 1 = Slight chance of dozing 2 = Moderate chance of dozing 3 = High chance of dozing
Sitting and talking to someone	0 = No chance of dozing 1 = Slight chance of dozing 2 = Moderate chance of dozing 3 = High chance of dozing
Sitting quietly after a lunch without alcohol	0 = No chance of dozing 1 = Slight chance of dozing 2 = Moderate chance of dozing 3 = High chance of dozing
In a car, while stopped for a few minutes in traffic	0 = No chance of dozing 1 = Slight chance of dozing 2 = Moderate chance of dozing 3 = High chance of dozing
[a]A total score of 10 or more from the eight criteria reflects above normal daytime sleepiness and need for further evaluation.	
Source: [47]	*Table 3*

homes (e.g., with extended family of many generations) are associated with poor limit setting and negative sleep-onset cues. Children should also be carefully screened for comorbid medical and psychiatric conditions that may have gone unnoticed. The diagnostic criteria for adults and children are shown in ***Table 2***.

Subjective assessment with a sleepiness instrument, such as the Epworth Sleepiness Scale (***Table 3***), may be helpful to ascertain the patient's degree of impaired sleep, but laboratory testing to measure sleepiness (e.g., the Maintenance of Wakefulness Test) usually does not show greater sleepiness in this cohort compared with healthy individuals [44]. The Epworth Sleepiness Scale has been found to be particularly effective for identifying cases of insomnia and less useful for diagnosing other sleep disorders [45]. Sleep studies are not typically needed to make a diagnosis, but polysomnography may reveal poor sleep continuity (e.g., decreased sleep efficiency, intermittent wakefulness) and more stage 1 sleep and limited stage 3 sleep [44; 46]. As noted, many persons with insomnia sleep better outside their own bed, and overnight laboratory testing may not provide significant data. Polysomnographic results also vary considerably from night to night in these patients [44]. Polysomnography is recommended for elderly individuals, as they are more prone to having identifiable etiologies of insomnia.

Treatment

Approximately 7 of 10 individuals with persistent insomnia struggle with insomnia after one year of treatment, and half still have insomnia three years later [2]. Complications of chronic insomnia include increased risk of depression, hypertension, work disability, and protracted use of prescription or over-the-counter sleep aids. Therefore, effective professional therapies are needed to avoid dangerous comorbidities and adverse drug effects. Additionally, managing comorbid medical and psychologic conditions with sleep-disrupting effects is necessary for these patients.

Sleep Hygiene

Management of chronic insomnia centers on behavior and lifestyle modification combined with counseling and instruction in effective sleep hygiene practices. Some of the foremost behaviors patients should modify or adhere to include keeping a consistent sleep schedule (i.e., going to bed at the same time each night and waking up at the same time each morning), devoting at least seven to eight hours each night to sleep, and creating and maintaining a bedtime ritual [48]. The optimum sleep time varies among individuals, but those with persistent excessive daytime sleepiness should sleep a minimum of six to eight hours.

Establishing a bedtime ritual involves deciding upon an activity or series of activities that provide conditioned sleep cues and consistently repeating those activities each night. The first part of the ritual should involve quitting challenging, engaging, or stressful tasks (e.g., paying bills, playing video games, watching television) and resolving any lingering worries (e.g., quarrels, dwelling problems). Some people find that if tasks are incomplete or issues are left unresolved, making a to-do list for the next day will help to clear their mind [48]. Next, patients should focus on relaxation for 20 or 30 minutes. During this time, they might read, listen to relaxing music, take a warm bath, or practice meditation and/or deep-breathing exercises. There are many other lifestyle modifications that can reduce the likelihood of developing a sleep disorder or can lead to a reduction of symptoms of an existing disorder. The following guidelines are all components of proper sleep hygiene and should be included as part of patient education for any sleep disorder [11; 48]:

- Large, heavy meals should be avoided late in the day, as should spicy, new, or exotic foods.
- Alcohol, caffeine, and nicotine should be avoided for at least four to six hours before bedtime. Alcohol initially acts as a sedative, but as the effect wears off, it can cause individuals to wake during the night. Chocolate, coffee, tea, and many other beverages contain caffeine and should be avoided at night.
- Long naps should not be part of a normal day. Occasional, light (30-minute) naps are permissible, but regular naps interrupt the sleep-wake cycle and can make falling asleep difficult at night. Patients should be able to remain awake throughout the day, and if this is not possible, this indicates insufficient sleep and/or a sleep disorder.
- Upon waking in the morning, individuals should seek out sunlight. Exposure to bright sunlight helps regulate the sleep-wake cycle. This is especially important for older adults and those who do not leave the house regularly.
- Patients should be encouraged to engage in at least 20 minutes of moderate-intensity exercise per day, a minimum of two to three hours before bedtime. Vigorous exercise is best performed in the afternoon or earlier in the day, while relaxing exercises (e.g., deep breathing, light yoga, meditation) may be performed before bedtime. Exercise performed earlier in the day helps deepen sleep.
- The bed should be used only for sleep and sex. Patients who do not fall asleep within 15 to 20 minutes of being in bed should get out of bed and engage in an uncomplicated or relaxing activity in low-light conditions until they feel drowsy. Taking a bath, reading, or having a small snack is recommended; watching television, doing work, or engaging in other mentally engaging activities is not. One should not lie in bed trying to force sleep.

The following changes to the sleeping environment have also been shown to promote sleep [48]:

- Keep the bedroom at a cool, yet comfortable, temperature. Use blankets rather than a heater for warmth, as cooler room temperatures lead to better sleep.
- Remove the television from the bedroom. Television programs and commercials are designed to be engaging and/or provocative and can keep individuals awake for many hours. Additionally, darkness is necessary to stimulate melatonin production, and light from the television can be disruptive if left on all night.
- Keep the bedroom as dark, quiet, and relaxing as possible. Ensure that bedding is comfortable. Use an eye shade or thick curtains to block out early morning sunlight, streetlights, and headlights. Some people find earplugs useful, and others use white noise or other machines to block out aberrant sounds.

A sleep hygiene regimen is a universally applicable prevention and treatment strategy that can improve sleep quality for those with and without a specific sleep disorder. Most sleep experts recommend that sleep hygiene be used as an adjunct to treatment for sleep disorders [2]. Despite limited research supporting the role of proper sleep hygiene in patients with insomnia, many patients will find these suggestions helpful. It has been found that individuals with chronic insomnia who are highly aware of poor sleep hygiene practices may be the most indifferent toward making changes [2].

Cognitive-Behavioral Therapy and Other Modalities

Certain forms of chronic insomnia tend to be less amenable to control with simple nonpharmacologic and brief sedative-hypnotic modes of treatment. Some form of cognitive-behavioral therapy (CBT), utilizing stimulus control, relaxation training, and sleep restriction therapies, sequentially or in combination, achieves the best results [46; 49]. Stimulus control therapy, which is akin to maintaining strict sleep hygiene, has been extensively studied and is the most recommended modality for initial insomnia treatment [43]. However, because sleep cues and other practices learned with sleep hygiene/stimulus control may become (or may already be) a cause of arousal, it is unlikely that all clinical subtypes will benefit significantly from this form of therapy.

The effectiveness of CBT for psychophysiologic insomnia has been demonstrated in several studies [43; 49; 50; 51]. Patients also tend to prefer CBT over pharmacologic options and other forms of psychotherapy [51]. Relaxation techniques (e.g., biofeedback, breath counting/deep breathing, meditation, progressive relaxation) can be an effective adjunct to CBT [46; 52]. Progressive relaxation can be particularly effective in patients who somatize stress into physical tension. This form of therapy involves tensing and relaxing individual muscle groups while breathing deeply, starting from the toes, working progressively through the calves, thighs, stomach, shoulders, hands, arms, and neck, and ending with the facial muscles. Deep breathing exercises use slow, controlled breaths (while counting) to "quiet" racing thoughts; if the mind wanders from counting breaths, patients should resume counting and eventually they should fall asleep [52].

Sleep restriction is also a useful form of therapy [52; 53]. This technique is based on the observation of deeper, more consolidated sleep in sleep-deprived test subjects. Through this paradoxical approach, patients learn to associate time spent in bed with time spent sleeping [54]. The first step is for patients to keep a sleep log for two weeks to determine their average total sleep time (i.e., average amount of time asleep in bed); 30 minutes is added to this time to establish the time they will be allowed in bed [55]. For example, if the patient's average total sleep time is 5 hours, the allowed time in bed will be 5.5 hours. Next, a wake time is set based upon when the patient needs to start their day (e.g., 6:30 a.m.), and the bed time is set by counting backward based on the time in bed allowance (e.g., 1:00 a.m.). Regardless of how sleepy the patient feels, he or she must not nap or get into bed before the prescribed bedtime. Upon waking, the patient should expose his or her eyes to bright light (daylight whenever possible) to reinforce the sleep/wake cycle [55]. If after two weeks the patient feels tired during the day, they may add 15 minutes to the sleep allowance, and every successive week they may add an additional 15 minutes until they are able to get to sleep easily, are sleeping well throughout the night, and feel rested during the day [55]. The minimum amount of sleep needed to achieve these goals is recommended, and a consistent sleep and wake time must be maintained. This therapy should be discontinued if job performance or safety is compromised due to excessive daytime sleepiness.

Pharmacologic Options

For some patients, CBT in combination with a pharmacologic agent, administered over six to eight weeks, is an effective strategy. The primary pharmacologic option for patients with chronic insomnia disorders is the administration of sedative-hypnotic drugs at night (e.g., eszopiclone, ramelteon, triazolam, zaleplon, zolpidem). However, long-term treatment with sedative-hypnotics is associated with a high incidence of adverse effects, including cognitive impairment, constipation, dizziness, headache, heartburn, the development of parasomnias (e.g., sleepwalking, sleep driving), and reduced respiratory drive [50]. If used, the lowest effective dose is recommended to reduce the incidence of these effects [50]. Additionally, AASM guidelines for the pharmacologic treatment of chronic insomnia in adults provide "weak" recommendations for the agents reviewed. AASM emphasizes that this grade does not indicate that the agents are ineffective but rather reflects a "lower degree of certainty in the outcome and appropriateness of the patient-care strategy for all patients" [56]. Patients should be cautioned not to combine these medications with alcohol or other central nervous system (CNS) depressants, as their combination can cause increased liver toxicity and drastically reduced cognitive and psychomotor functioning [57].

Different sedative-hypnotics are indicated for various sleep difficulties. Zaleplon is fast acting, but has a short half-life; this drug may be best for patients who experience night awakenings with difficulty returning to sleep [58]. Zolpidem has a rapid onset and short-half life as well; patients with difficulty falling asleep may benefit from this drug. A controlled-release version is also available. Eszopiclone has a slow onset and long duration of action and is indicated for patients with difficulty staying asleep and with perception of poor sleep quality [57].

The American Academy of Sleep Medicine recommends the following agents be considered for the treatment of chronic sleep-onset insomnia:

- Eszopiclone
- Zaleplon
- Zolpidem
- Triazolam
- Temazepam
- Ramelteon

(https://jcsm.aasm.org/doi/10.5664/jcsm.6470. Last accessed December 7, 2021.)

Strength of Recommendation: Weak (a lower degree of certainty in the outcome and appropriateness of the patient-care strategy for all patients)

Hypnotic drugs are best utilized when nonpharmacologic measures do not achieve symptom reduction, when insomnia causes serious impairment, or when an immediate response is desired [54]. The following are best practice guidelines regarding the prescription and use of sedative-hypnotics [54; 59]:

- Avoid these agents or exercise caution if patient has a history of substance abuse, acute cerebrovascular accident, myasthenia gravis, or respiratory impairment.
- Prescribe hypnotics only for short durations (one to two weeks) and intermittently (based on symptom resolution).
- Watch for requests for escalating doses or resistance to tapering/discontinuing hypnotic.
- Hypnotics should be discontinued gradually. Be alert for adverse effects (especially rebound insomnia) and withdrawal phenomena when titrating doses.
- The lowest effective dose should be prescribed.

Herbal and Hormonal Supplements

A variety of herbal, hormonal, and dietary supplements have been marketed as sleep aides, with scant evidence of significant benefit. Melatonin, a brain hormone produced by the pineal gland, does have some function in regulating the normal sleep cycle, and melatonin supplementation may be of benefit to a subset of patients with delayed sleep phase syndrome (a disturbance of the circadian rhythm). However, it does not appear to be helpful for most people who have insomnia. It is safe when used in modest dosage (2–3 mg per night) for short periods (three months or less) [60]. Melatonin is unregulated by the U.S. Food and Drug Administration (FDA); formulations vary in strength, and higher doses can lead to adverse side effects (e.g., disrupted sleep, fatigue, headache) [57]. AASM does not recommend melatonin for sleep onset or sleep maintenance insomnia in adults [56].

Valerian is a popular herbal product commonly used to self-treat insomnia. It causes CNS sedation by inhibiting the breakdown of certain chemical mediators within the brain. Clinical trials have shown minimal effectiveness at best [61]. This product is also unregulated by the FDA. Daytime drowsiness and rare instances of liver toxicity have been observed in association with its use. AASM does not recommend valerian for sleep onset or sleep maintenance insomnia in adults [56].

SHORT-TERM INSOMNIA DISORDER

The essential features and diagnostic criteria of short-term insomnia disorder are similar to those of chronic insomnia disorder, minus the frequency and duration criteria. Insomnia is considered short-term if lasting fewer than three months [2; 46]. The differential diagnosis should exclude circadian rhythm sleep-wake disorders caused by jet lag or rotating shift work. These are caused when the established circadian rhythm is decoupled from the normal sleep-wake schedule. Individuals with short-term insomnia experience sleep difficulties within their normal sleep-wake schedule.

Approximately 15% to 20% of individuals experience short-term insomnia each year [2]. The frequency is higher in women than in men and in older age groups. Although many cases of short-term insomnia resolve over time or when the stressor is removed, a significant number of cases progress to chronic insomnia, as discussed. Treatment of short-term insomnia should focus on good sleep hygiene, but CBT and pharmacotherapy may be warranted in order to ensure non-progression to chronic insomnia [46].

SLEEP-RELATED BREATHING DISORDERS

As the name suggests, the ICSD-3 category of sleep-related breathing disorders includes any respiratory disorders that occur during sleep. This category is further organized into the following subgroups and disorders [2]:

- Obstructive sleep apnea syndromes (adult and pediatric) caused by upper airway obstruction.
- Central sleep apnea syndromes, which are caused by cardiac or nervous system dysfunction. The eight disorders in this group are:
  - Central sleep apnea with Cheyne-Stokes breathing
  - Central apnea due to medical condition without Cheyne-Stokes breathing
  - Central sleep apnea due to high altitude periodic breathing
  - Central sleep apnea due to a medication or substance
  - Primary central sleep apnea
  - Primary central sleep apnea of infancy
  - Primary central sleep apnea of prematurity
  - Treatment-emergent central sleep apnea
- Sleep-related hypoventilation disorders, including obesity hypoventilation syndrome, congenital central alveolar hypoventilation syndrome, late-onset central hypoventilation with hypothalamic dysfunction, idiopathic central alveolar hypoventilation, sleep-related hypoventilation due to medication or substance, and sleep-related hypoventilation due to a medical disorder
- Sleep-related hypoxemia disorder, including sleep-related hypoxemia
- Isolated symptoms and normal variants

Only obstructive sleep apnea syndrome will be discussed in detail in this section, as the other sleep-related breathing disorders are comparatively rare and/or mainly associated with other medical conditions. For example, central sleep apnea due to Cheyne-Stokes breathing is primarily associated with congestive heart failure and stroke, and primary

central sleep apneas of infancy or prematurity are associated with premature birth and low birth weight, occurring in 25% of infants weighing <2,500 g and 84% of infants weighing <1,000 g [2]. Others are extremely rare. It is estimated that there are perhaps a total of 200 congenital central alveolar hypoventilation syndrome cases worldwide [2].

OBSTRUCTIVE SLEEP APNEA SYNDROME

Obstructive sleep apnea syndrome is characterized by recurrent upper airway obstruction caused by repetitive narrowing or collapse of the pharyngeal airway during sleep, resulting in reductions (hypopneas) or pauses (apneas) in breathing, in spite of abdominal and chest movements; reduced blood oxygen saturation (less than 50% in some patients); and frequent arousals (potentially hundreds per night) [2; 62]. Loud snoring coupled with periods of silence lasting at least 10 seconds, but often 20 to 30 seconds, are features of the syndrome. Gasping may occur instead of snoring, especially in children and adolescents; however, most patients with obstructive sleep apnea begin loud snoring in childhood. Patients may have grown accustomed to the excessive sleepiness, mental dullness, depression, frequent night awakenings, dry mouth, and morning headaches that accompany the disorder [2]. Alcohol use can increase snoring intensity, as can excess weight gain and obesity. Patients with obstructive sleep apnea often have nasopharyngeal abnormalities [2]. Adult patients typically have a generalized narrowing of the upper airway, and enlarged adenoids and/or tonsils are commonly seen in children.

Individuals may experience bouts of acute obstructive sleep apnea as the result of an inflammation-causing illness (e.g., Epstein-Barr virus, upper respiratory infection) or as a result of the ingestion of alcohol, drugs, or medications that cause relaxed muscle tone (especially in the genioglossus and geniohyoideus muscles). Individuals with occasional symptoms do not typically seek or need extensive evaluation or care for sleep apnea other than treatment for a primary condition or cessation of the substance causing airway restriction [2]. On the other hand, patients for whom the disorder is chronic (i.e., six months or longer) require careful evaluation and prompt initiation of treatment, as even mild cases of chronic obstructive sleep apnea have been consistently and independently linked to cardiac arrhythmias, cardiovascular disease, hypertension, stroke, motor vehicle accidents, and diminished quality of life [63; 64].

If a patient presents with complaints of excessive daytime sleepiness or non-restful sleep and a history of snoring, obstructive sleep apnea should be suspected. A comprehensive medical history and physical evaluation should be obtained, and various objective sleep studies (e.g., polysomnography, portable monitors, MSLT) should be completed to confirm the diagnosis. The AHI scale has been developed to quantify and standardize the degree of obstructive sleep apnea severity. The score is determined by adding the number of apnea and hypopnea events during a patient's overnight sleep study, dividing the total number of events by the minutes of sleep, and finally multiplying the result by 60. For example, if a patient sleeps 8 hours (480 minutes) and has 120 apnea events and 80 hypopnea events (200 total events), the calculation for this patient would be 200 events ÷ 480 minutes × 60, for an AHI score of 25. A normal cutoff for AHI has never been defined in an epidemiologic study of healthy people. Most sleep centers use a cutoff of 5 to 10 episodes per hour. The severity of obstructive sleep apnea is arbitrarily defined and differs widely between centers. Recommendations for cutoff levels on AHI include 5 to 15 episodes per hour for mild, 15 to 30 episodes per hour for moderate, and more than 30 episodes per hour for severe [65]. In the example, the patient has an AHI score of 25, or moderate obstructive sleep apnea.

Epidemiology

Obstructive sleep apnea is by far the most common sleep-related breathing disorder [62]. Using the AASM criteria, it is estimated that 1 in 5 American adults has at least mild obstructive sleep apnea and 1 in 15 has at least moderate obstructive sleep apnea [63]. The incidence of the disorder increases with age, and it is two to three times more common in men than in women [62; 63; 66]. The estimated incidence among various age-groups is [62; 66]:

- Children: 2% to 8% among both sexes
- 30 to 60 years of age: 4% to 9% of women, 9% to 24% of men
- 65 to 99 years of age (with an AHI greater than 10): 56% of women, 70% of men

Differences in incidence among racial and ethnic groups have not been extensively studied. Although race is thought to be an important risk factor for sleep disordered breathing, at this time it is not certain what role race or ethnicity plays in the development of obstructive sleep apnea. Researchers have attempted to link occurrence of the disorder to racial craniofacial differences and variations in body mass trends or fat distribution, with little replicable data to support their hypotheses [66]. Again, this may be due to a lack of research that accounts for race in the United States and other Western countries and limited research of the disorder in Africa, Asia, and the Pacific Islands.

Risk Factors

Many risk factors have been theoretically linked to obstructive sleep apnea. The most widespread factors are alcohol consumption, smoking, overweight and obesity, and hormonal changes related to pregnancy, menopause, and polycystic ovary syndrome [63]. There are conflicting studies for each of these theories, and only overweight and obesity is considered a statistically significant risk factor.

Excess body weight is the strongest risk factor for obstructive sleep apnea in the general population, and most (though not all) patients who present with the disorder are heavier than

normal weight [2]. The overweight and obesity epidemic in the United States has caused a concurrent rise in the prevalence of sleep disordered breathing, but the mechanisms involved are still unclear [67]. Hypotheses for the pathophysiology of overweight and obesity in the disorder include distorted upper airway structure and function (caused by altered neck morphology), an altered relationship between respiratory drive and load compensation, and intensification of apnea/hypopnea events through obesity-related decreases in functional residual capacity and increased whole-body oxygen demand [63; 68; 69]. Other obesity-related conditions, including insulin resistance, generalized inflammation, hypoactive hypothalamic corticotropin-releasing hormone neurons, and visceral adiposity, have been suggested as factors in the development of obstructive sleep apnea following excessive weight gain [70]. Individuals with an "apple-shaped" body (i.e., central adiposity) or who have a greater neck circumference are thought to be more affected than those who are "pear shaped" (i.e., gynoid adiposity), but there is little concrete evidence to support this idea [67].

Obesity may also be a risk factor for obstructive sleep apnea in children and adolescents. One study found a relative risk 4.59 times higher in obese children 2 to 18 years of age compared with normal weight controls [71].

Despite the lack of consensus regarding the role of excess body weight in the pathogenesis of obstructive sleep apnea, studies have shown a strong positive correlation between body mass index (BMI) and AHI [63; 68; 72]. A decade-long Wisconsin study of 690 randomly selected participants (mean age: 46 years) found that a 10% weight gain yielded a six-fold increase in the odds of developing moderate-to-severe sleep disordered breathing compared with individuals who maintained a steady weight [67]. Those who lost 10% of their initial weight during the study period lowered their AHI score by an average of 26% (range: 18% to 34%). Several small-scale studies have shown improvements in obstructive sleep apnea symptoms following surgical weight-loss interventions. Body mass reduction following bariatric surgery can cause the most dramatic (though possibly short-term) decrease in AHI score [63; 64; 68; 72].

Evaluation and Diagnosis

History and Physical Examination

The diagnosis of obstructive sleep apnea is usually made in one of three settings: a general, routine health evaluation, a screening of high-risk patients, or an evaluation suggestive of obstructive sleep apnea [41]. High-risk groups include individuals who are obese or are being evaluated for bariatric surgery; those with atrial fibrillation, congestive heart failure, treatment-refractory hypertension, nocturnal dysrhythmias, pulmonary hypertension, type 2 diabetes, and/or stroke; and high-risk driving populations (i.e., commercial truck drivers). During the initial evaluation, a history of snoring and daytime sleepiness should be taken, along with an assessment of BMI, blood pressure, maxillofacial irregularities (e.g., retrognathia), and upper airway restriction (e.g., large adenoids/tonsils).

A detailed sleep history should be obtained, including evaluation for [41]:

- Snoring
- Witnessed apneas
- Gasping/choking episodes
- Excessive sleepiness not explained by other factors, including assessment of sleepiness severity by the Epworth Sleepiness Scale
- Total sleep amount
- Nocturia
- Morning headaches
- Sleep fragmentation/sleep maintenance insomnia
- Decreased concentration and memory

Any of the previously discussed complications associated with obstructive sleep apnea (e.g., hypertension, stroke, motor vehicle accidents) should be documented. The physical examination may reveal common physical traits associated with obstructive sleep apnea, including [41]:

- Increased neck circumference (>17 inches in men, >16 inches in women)
- BMI ≥30
- Large tongue (modified Mallampati score of 3 or 4)
- Lateral peritonsillar narrowing
- Tonsillar hypertrophy
- Elongated/enlarged uvula
- High arched/narrow hard palate
- Nasal abnormalities (e.g., deviation, polyps, valve abnormalities, turbinate hypertrophy)
- Retrognathia
- Overjet (protrusion of the upper teeth)

The differential diagnosis of obstructive sleep apnea in adults includes nonpathologic snoring, panic attacks, laryngospasm related to gastroesophageal reflux, and dyspnea associated with pulmonary edema [2].

Testing

Objective testing with a standardized method follows suspicion of obstructive sleep apnea to confirm the diagnosis and guide the initiation of treatment. In-laboratory polysomnography is the preferred method of objective sleep testing and is recommended for most patients [41]. At-home testing with portable monitors may be used prior to laboratory testing or to confirm the efficacy of treatments, but it should not be used for individuals with a high degree of comorbidity unless in-laboratory monitoring is not feasible due to safety or mobility issues.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American College of Physicians recommends polysomnography for diagnostic testing in patients suspected of obstructive sleep apnea. Portable sleep monitors are recommended for patients without serious comorbidities as an alternative to polysomnography when it is not available for diagnostic testing.

(https://www.acpjournals.org/doi/10.7326/M12-3187. Last accessed December 7, 2021.)

Level of Evidence: Moderate-quality evidence (Randomized, controlled trials with important limitations)

Diagnostic Criteria for Adult Patients

The AASM has established diagnostic criteria for adults suspected of having obstructive sleep apnea. In all cases, the disorder must not be better explained by another current sleep disorder, medical or neurologic disorder, medication use, or substance use disorder. In addition, patients must display the following signs and symptoms [2]:

- Polysomnographic recording or out of center sleep testing showing 15 or more predominantly obstructive respiratory events (i.e., apneas, hypopneas, or respiratory effort-related arousals) per hour of sleep

OR

- Polysomnographic recording or out of center sleep testing showing five or more predominantly obstructive respiratory events per hour of sleep
- At least one of the following:
  - Complaints of daytime sleepiness, unrefreshing sleep, unintentional sleep episodes during wakefulness, fatigue, or insomnia
  - Waking with breath holding, choking, or gasping
  - Bed partner or observer reports loud snoring, breath interruptions, or both
  - Diagnosis of hypertension, mood disorder, cognitive dysfunction, coronary artery disease, stroke, congestive heart failure, atrial fibrillation, or type 2 diabetes

Diagnostic Criteria for Pediatric Patients

The criteria established to diagnose obstructive sleep apnea in adults have been found to be insufficient to identify children with the disorder. For these patients, parents or caretakers must report a history of labored breathing, snoring, or both, and observation of at least one of the following must be made to diagnose pediatric obstructive sleep apnea [2]:

- Snoring
- Labored, paradoxical, or obstructed breathing during sleep
- Sleepiness
- Hyperactivity
- Behavioral problems
- Learning problems

Differentiating obstructive sleep apnea from primary snoring requires the use of polysomnography. Further, one (or more) scorable event per hour must be recorded during the sleep study. For diagnosis of obstructive sleep apnea in children, polysomnographic findings must include [2]:

- One or more obstructive apneas, mixed apneas, or hypopneas, per hour of sleep

OR

- A pattern of obstructive hypoventilation, defined as at least 25% of total sleep time with hypercapnia ($PaCO_2$ > 50 mm Hg) in association with one or more of:
  - Snoring
  - Flattening of the inspiratory nasal pressure waveform
  - Paradoxical thoracoabdominal motion

The disorder must also not be better explained by any other medical condition, including another sleep disorder.

Treatment

Due to the chronic nature of the disorder, obstructive sleep apnea treatment is typically long-term and includes behavioral, medical, and surgical options. Patient education regarding the clinical consequences, natural history, pathophysiology, and risk factors of the disorder, and general information, such as alcohol avoidance, risk factor modification, medication effects, weight loss, sleep position, and drowsy driving, should be given upon diagnosis. The goals of treatment are to improve breathing during sleep, to lessen or prevent the sequelae associated with excessive daytime sleepiness and the disorder itself, and patient and partner satisfaction [41].

Positive Airway Pressure Therapy

According to the American College of Physicians (ACP), the principal initial treatment for obstructive sleep apnea is positive airway pressure (PAP) therapy, which uses forced air to maintain a patent pharyngeal airway [73]. This therapy may be provided in one of three modes: continuous (CPAP), bilevel (BPAP), or autotitrating (APAP), all with or without pressure relief (i.e., partial pressure reduction during expiration) [41; 71]. CPAP is the standard mode of PAP therapy; BPAP and APAP are used when CPAP cannot be tolerated. CPAP therapy is also recommended for patients with mild obstructive sleep apnea who have failed to improve with behavior modification or who are unable to enact lifestyle

changes and who have symptoms that affect their ability to perform daily tasks and impact their quality of life [71].

CPAP appliances consist of a mask or other device that fits over the nose or the nose and mouth, a tube that connects to the mask, and a motor that blows air into the tube [74]. A humidifier and/or heater can be used to condition the device air and lessen or prevent complications, such as throat irritation, nasal dryness, and nasal bleeding. Many patients have difficulty adjusting to wearing the mask and may feel confined during sleep. Periodically wearing the mask during the day, trying CPAP while awake, or using relaxation exercises should be recommended to help in getting comfortable with the device [74]. Newer machines have a "ramp" feature that slowly builds to the prescribed pressure level, which can help with adjusting to the unnatural feeling that CPAP can create.

The clinical effectiveness of CPAP therapy on measures of self-reported daytime sleepiness, fatigue, cognitive function, and depression is supported by evidence. However, the effect on other measures, such as hypertension and cardiovascular events, is unclear [74]. A 2012 clinical trial summary showed that 19% of patients in the CPAP study group developed hypertension, compared with 22% in the control group (dietary and sleep hygiene counseling), and 8% of patients using CPAP had a cardiovascular event, compared with 8% in the control [75]. Although the authors stated that CPAP therapy outcomes failed to reach statistical significance in reduction of these two measures, the small study size may have had limited power to detect a significant difference. A meta-analysis that included 3,780 patients found that, compared with medical therapy alone, CPAP was not associated with a reduced risk of major adverse cardiac events. Improved cardiac outcomes were observed only in a subgroup of patients who wore the CPAP mask for more than four hours at a time [76]. A 2021 meta-analysis that included 2,590 participants found a significant association between use of CPAP and reduced risk of major adverse cardiovascular events, particularly among participants with an AHI less than 30 events per hour [77]. Still, the authors concluded that more research is needed to confirm this benefit.

Oral Appliances

An oral appliance is a custom-fit, molded mouthpiece that is fitted by a dental professional to enlarge the upper airway and/or decrease upper airway collapsibility. There are two types of oral appliances: mandibular advancement devices (MADs), which advance the mandible with respect to the resting position and cover the upper and lower teeth, and tongue-retaining devices, which do not reposition the mandible but hold the tongue forward relative to the resting position. The ACP recommends MADs as an alternative for patients who cannot tolerate or would prefer not to use PAP therapy [73]. A complete dental history and dental examination for appraisal of characteristic patterns of wear from nocturnal bruxism; soft tissue, periodontal, and temporomandibular joint (TMJ) assessment; evaluation of occlusion; and resolution of dental pathology precludes the fitting of the appliance. The type employed will be based on a patient's individual anatomy, preferences, and dental assessment. MADs require satisfactory jaw range of motion, no important TMJ disorder, and enough healthy teeth upon which to seat the oral appliance.

The American Academy of Sleep Medicine recommends sleep physicians consider prescription of oral appliances, rather than no treatment, for adult patients with obstructive sleep apnea who are intolerant of CPAP therapy or prefer alternate therapy.

(https://jcsm.aasm.org/doi/10.5664/jcsm.4858. Last accessed December 7, 2021.)

Level of Evidence: Moderate

A 2006 Cochrane Database review found that oral appliances had similar effectiveness on self-reported outcome measures (e.g., subjective sleepiness, depression) as CPAP therapy but were inferior in reducing respiratory disturbances among most patients [78]. Patients expressed a strong preference for the oral appliances. However, participants were more likely to withdraw on oral appliances than on CPAP therapy. Oral appliance therapy is recommended for patients with mild obstructive sleep apnea who fail behavioral treatments or for patients with mild-to-moderate obstructive sleep apnea who prefer the option over CPAP, who are not candidates for CPAP, or who do not respond to CPAP, or for those carefully selected patients in whom they are as effective in reducing daytime symptoms and AHI score [41; 78].

Behavior Modification

There have been no large-scale clinical trials of dietary, exercise, medication, or surgical weight-loss interventions on outcomes in patients with sleep disordered breathing. However, the ACP recommends that all overweight and obese patients diagnosed with obstructive sleep apnea be encouraged to lose weight [73]. Many small-scale studies have shown that BMI reduction (by any means) is effective at reducing the number and duration of apnea and hypopnea events [64]. Other behavioral options include positional therapy and avoidance of alcohol and sedative drugs.

A 10% weight loss can considerably reduce the total number of obstructive events per night, and all patients should be strongly encouraged to achieve a BMI ≤25 through a combination of diet and exercise to improve obstructive sleep apnea symptoms and lessen the risk of comorbidities [41; 67]. Subsequent to body mass reduction, AHI should be reassessed using in-lab polysomnography to determine whether PAP adjustments are needed or if PAP therapy may be discontinued altogether. Because significant and lasting weight reduction is typically not achieved by most patients,

COMMON SURGICAL PROCEDURES FOR OBSTRUCTIVE SLEEP APNEA BY SITE	
Site	**Procedure**
Upper airway	Tracheotomy
Nasal	Septoplasty Functional rhinoplasty Nasal valve surgery Turbinate reduction Nasal polypectomy Endoscopic procedures
Oral, oropharyngeal, and nasopharyngeal	Uvulopalatopharyngoplasty and variations Palatal advancement pharyngoplasty Tonsillectomy and/or adenoidectomy Excision of tori mandibularis Palatal implants
Hypopharyngeal	Tongue reduction Partial glossectomy Radiofrequency ablation Lingual tonsillectomy Tongue advancement/stabilization Genioglossus advancement Hyoid suspension Mandibular advancement Tongue suspension
Laryngeal	Epiglottoplasty Hyoid suspension
Global airway	Maxillomandibular advancement Bariatric surgery
Source: [41]	*Table 4*

especially with a dietary component alone, other treatment strategies should be employed simultaneously [41]. Even sustained weight loss does not often fully alleviate the disorder.

A supine sleep position is most likely to affect breathing, and maintaining a non-supine position throughout sleep helps to keep the airway patent in some patients [41]. Identification of individuals who have a low AHI in a non-supine position is necessary before positional therapy is initiated. If appropriate, a device (e.g., alarm, backpack, tennis ball, pillow) may be employed to keep the patient from sleeping on his or her back.

Surgical Treatment

Before the widespread use of PAP therapy, surgery was the primary treatment for obstructive sleep apnea, and it is still indicated for certain cases. Many surgical options involving reconstruction (or bypass) of the upper airway can be used to reduce the severity of obstructive sleep apnea symptoms and increase the effectiveness of behavioral and medical treatments (***Table 4***); however, it is beyond the scope of this course to cover the details of each procedure. Bariatric weight-loss surgery is also considered a treatment for obstructive sleep apnea and is indicated for patients with a BMI ≥40 or BMI ≥35 with significant comorbidities and failure to achieve weight loss with diet and exercise [41].

After a diagnosis of obstructive sleep apnea has been established, it should be determined if patients are appropriate candidates for surgery as a primary, secondary, or adjunct treatment [79]. Candidates should also be screened for comorbidities that would affect the outcome of surgery. This and individual anatomy will dictate which option is chosen. Patients with obstructive sleep apnea who have gross anatomic abnormalities that are correctable (e.g., tonsillar and/or adenoidal hypertrophy, collapse or narrowing of the retropalatal or retrolingual areas) should be considered for primary surgical treatment regardless of the severity of the disorder [41]. Surgery as secondary treatment should be considered for patients who have failed to improve with PAP therapy or with an oral appliance or who cannot tolerate either modality. Upon examination of the upper airway, a patient with a gross obstruction that is deemed likely to interfere with the placement, effectiveness, or tolerance of either oral appliances or PAP should be considered a candidate for surgery as an adjunct treatment [41].

The goals, benefits, risks, complications, and possible side effects of the chosen procedure(s) should be discussed, and the willingness to undergo surgical therapy should also be assessed. Although certain procedures (e.g., maxillomandibular advancement, radiofrequency ablation) seem to be effective in reducing AHI score, evidence for most procedures is of low quality and long-term data regarding effectiveness and sequelae is not available [79]. Patients should be informed that most surgeries will not cure obstructive sleep apnea but may improve clinical outcomes (e.g., cardiovascular risk, daytime sleepiness, mortality) [41]. The exception is tracheotomy, which can completely eliminate obstructive sleep apnea but not improve blood oxygen saturation or resolve other symptoms of hypoventilation syndrome. Tracheotomy for obstructive sleep apnea is typically only performed when all other options have been exhausted, when clinically urgent, or in special populations (e.g., patients with Alzheimer disease, Down syndrome, or mental and physical handicaps), as it is a radical procedure that requires a high level of care and lifestyle modification [79].

Pharmacologic and Oxygen Therapies

There are no effective pharmacotherapies for obstructive sleep apnea with the exception of medications used to treat conditions (e.g., hypothyroidism, acromegaly) that can precipitate obstructive sleep apnea or that worsen symptoms of the disorder (e.g., rhinitis) [41]. Patients with persistent daytime sleepiness (despite well-documented improvement in AHI score with PAP or other treatments) may benefit from use of the analeptic modafinil. All other causes of daytime sleepiness must be ruled out and PAP therapy should not be discontinued when taking modafinil. This drug is also used for the treatment of narcolepsy and will be discussed in detail later in this course. In 2019, two drugs, solriamfetol (Sunosi) and pitolisant (Wakix), were approved by the FDA to improve wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea. [57; 80]. Solriamfetol, a dual dopamine-norepinephrine reuptake inhibitor, has exhibited robust efficacy in randomized controlled trials. Initial oral dosing is 37.5 mg once daily, titrated up to a maximum dose of 150 mg/day. The most common adverse reaction is headache [57]. Pitolisant is a histamine H3 receptor inverse agonist approved for the treatment of cataplexy or excessive daytime sleepiness in adults with narcolepsy. Initial oral dosing is 8.9 mg once daily for one week, then 17.8 mg once daily for one week. The dose may be further increased based on response and tolerability during the third week to a maximum dose of 35.6 mg once daily. As with solriamfetol, the most common adverse reaction is headache [57]. Oxygen therapy is not considered a useful treatment for obstructive sleep apnea, as it has been found that it can lengthen the duration of apneas [41]. However, it is sometimes used to relieve hypoxemia. Resolution of hypoxemia must be documented to justify continued use, especially in patients with comorbid respiratory disease who are at an increased risk of hypercapnia with oxygen therapy.

CENTRAL DISORDERS OF HYPERSOMNOLENCE

The ICSD-3 category of central disorders of hypersomnolence includes those that cause excessive daytime sleepiness as the primary complaint; circadian-rhythm shifts and disturbed nocturnal sleep must not be the cause of the primary symptom [2]. The eight disorders in this group are narcolepsy type 1 (with cataplexy); narcolepsy type 2 (without cataplexy); idiopathic hypersomnia, Kleine-Levin syndrome, hypersomnia due to a medical disorder; hypersomnia due to a medication or substance; hypersomnia associated with a psychiatric disorder, and insufficient sleep syndrome [2]. For simplification, the two types of narcolepsy will be discussed as one in the following section, as will idiopathic hypersomnia, along with a brief section on other ICSD-3 hypersomnias.

NARCOLEPSY

Narcolepsy is a primary disorder of the CNS characterized by recurring episodes (every two to three hours) of extreme sleepiness, sudden and irresistible sleep attacks, disturbed nighttime sleep, and memory problems resulting from sleep deficit [2; 81]. Sleep spells (or attacks) usually occur during activities or situations in which sleepiness is common (e.g., as a passenger, in a class with no participation, during movies) and last 10 to 20 minutes, on average. However, they may also occur at times when sleeping is not normal (e.g., while driving, eating, walking, or talking). Individuals will feel rested when they awake, but this sense of refreshment does not last long. Sleepiness soon returns, and the cycle repeats. The disorder strongly features SOREMPs and is associated with several pathologic REM sleep phenomena, including cataplexy, sleep paralysis, and hypnagogic/hypnopompic hallucinations [82].

Narcolepsy occurs in two basic subtypes: with cataplexy and without. Cataplexy is defined as a loss of bilateral muscle tone triggered by intense emotions with an exciting element (e.g., anger, elation, laughter, surprise, sexual arousal) [2; 81; 82]. All skeletal muscle groups may be involved, or the effects may be localized. Typical patterns include weakening of the eyelids, mouth, neck, waist, or upper or lower limbs. Smooth, cardiac, and oculomotor muscles are unaffected. The severity of cataplexy varies between individuals and can range from mild eye droop and slurred speech to buckling of the knees and complete postural collapse with fall. The episodes typically last from seconds to minutes. Recovery is usually immediate and complete, but episodes can be repetitive in some individuals if the emotional stimulus recurs, referred to as status cataplecticus, and in rare instances, recurrent attacks have been known to last for up to one hour [2]. Some patients experience cataplexy daily, while others may experience it less than monthly [81].

Most narcoleptic patients experience sleep paralysis, or an inability to speak or move for one to several minutes (up to one hour rarely) while transitioning into and out of sleep (hypnagogic and hypnopompic, respectively) [2; 82]. Like cataplexy, sleep paralysis is a pathologic version of REM sleep atonia and does not affect smooth, cardiac, or oculomotor muscles; however, a sensation of being unable to breathe often accompanies the episode. In cataplexy and sleep paralysis, extensor and flexor reflexes are both lost, which typically only occurs in healthy individuals during REM sleep [42]. A 2011 meta-analysis of 35 studies found that sleep paralysis is experienced by approximately 7.6% of the U.S. general population at some point in their lives, but up to 60% of patients with narcolepsy regularly experience the phenomenon [83; 84; 85]. Sleep paralysis is typically accompanied by hallucinations [82].

The hypnagogic and hypnopompic experiences (HHEs) that accompany sleep paralysis appear in three generalized categories but are overwhelmingly of the first type of hallucination, dubbed "Intruder." These hallucinations are described as a sensed evil, malevolent, or threatening presence [86; 87]. The second type, the "Incubus," is less common. Described as a demonic or alien being on/near the bed or on top of the body, it is associated with chest pressure, breathing difficulties, and/or pain. Pain is experienced by some individuals while attempting to move their limbs, and another subset may think their limbs are moving when they actually remain still (e.g., while fighting off a perceived threat) [86]. An extreme sense of dread or terror is usually felt during these two types of experiences. Individuals can misconstrue sounds and visions during HHEs (e.g., an object or a shadow may be seen as demon, but later they can reason the misinterpretation) or they may have full-blown, vivid hallucinations (e.g., interaction with beings they are convinced have an external source) [87]. Interestingly, descriptions of beings are consistent throughout history and across cultures, and it is thought that many alien, ghostly, and demonic assault, visitation, and possession incidents are derived from "Incubus"-type HHEs. The third type, "unusual bodily experiences," is infrequently encountered and is described as a flying/floating, out-of-body, or blissful experience without a frightening component [86].

Epidemiology

Narcolepsy is the second most common sleep-related disorder in the United States (after obstructive sleep apnea), affecting an estimated 1 in 2,000 individuals or an estimated 135,000 to 200,000 Americans [42]. Men and women are equally affected, but prevalence varies by race/ethnicity. For example, compared with the United States, narcolepsy is more common in Japan and less common in Israel. Narcolepsy with cataplexy is less common, estimated to affect 1 in 3,000 Americans [42]. The age of onset is typically between 7 and 25 years.

Risk Factors

The causes of narcolepsy are not well known, so it is difficult to determine the influencing factors. There is a heritable component that can predispose individuals to developing the disorder. Certain gene variants of the human leukocyte antigen (HLA) complex and its receptor, T-cell receptor alpha (TCRA), are strongly associated with narcolepsy [42]. Most (though not all) narcoleptic individuals possess the HLA-DR2 or HLA-DQB1*0602 phenotype, which are risk factors for autoimmune disease. However, inflammatory markers and signs/clinical features of inflammatory processes are typically not found in narcoleptics [88; 89; 90]. This suggests that if the disorder does have an autoimmune origin, the pathology is confined to the nervous system.

Researchers believe that individuals with the implicated subtypes of HLA and TCRA are more prone to an immune system attack on hypocretin-producing neurons in the hypothalamus [42; 82]. The neurotransmitter protein hypocretin regulates appetite, feeding, and sleep patterns, including keeping brain systems from unexpectedly shutting off while awake. People with narcolepsy with cataplexy (and a certain subset of individuals without cataplexy) typically have very low levels of hypocretin, which could explain why they develop narcolepsy and also the higher rate of obesity in this population [42; 82; 91].

Though a genetic predisposition does exist, it does not fully explain development of the disorder, as most individuals with the HLA/TCRA variants do not develop narcolepsy and some narcoleptics do not possess these subtypes. In certain rare instances, tumor growth or head trauma have led to narcolepsy [42]. Other factors, including environmental toxins, stress, dietary factors, changes to the sleep schedule, and hormonal changes, likely contribute to the development of the disorder. Infectious agents have been identified as triggers for narcolepsy, particularly *Streptococcus* spp. and the H1N1 influenza virus, but it is not yet known if the infections are direct triggers or if they indirectly increase susceptibility (e.g., due to the relaxed blood-brain barrier during fever) [42].

Diagnosis

As discussed, the most common presentation for all sleep disorders, including narcolepsy, is excessive daytime sleepiness. Cataplexy is rare without narcolepsy and is considered a positive indicator of the disorder [42]. If cataplexy is not present, all other causes of excessive sleepiness must be ruled out by collecting a thorough medical history and conducting an exhaustive clinical examination. The Epworth Sleepiness Scale can be used to identify excessive daytime sleepiness. For the diagnosis of narcolepsy to be confirmed, polysomnography and an MSLT should be performed in a sleep clinic. A polysomnographic study for narcolepsy is similar to an obstructive sleep apnea study. The MSLT will indicate shorter sleep latency periods in patients with narcolepsy compared with healthy individuals [42].

Laboratory testing may include cerebrospinal fluid (CSF) hypocretin-1 levels, but the value of this test is debated [2; 42; 92]. CSF hypocretin sampling is generally not recommended unless MSLTs are inconclusive or unavailable. This is because reduced or absent levels are usually only found in patients with cataplexy [42; 92]. Although most narcoleptic patients without cataplexy have normal hypocretin levels, there is a subset who is deficient, including individuals with the HLA-DR2 phenotype, those at a younger age at onset, and patients with shorter mean REM latency periods [91].

Treatment

Narcolepsy is incurable, and the loss of hypocretin in patients with cataplexy is believed to be irreversible [42]. However, there are several pharmacologic and behavioral treatment options that, when combined, can greatly reduce symptoms of the disorder and help improve patients' quality of life.

Pharmacologic Therapies

Traditional drug treatment options for narcolepsy have included CNS stimulants taken during the daytime to help patients remain alert, sedatives taken at night to help patients attain more restful sleep, and tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) to help control cataplexy, sleep paralysis, and HHEs [42; 93; 94]. Certain drugs have been found to exert multiple effects; for example, modafinil, a stimulant drug used to treat daytime sleepiness, may also exert antidepressant effects by modulating serotonin transmission [95]. These drug classes are still recommended for prescription today, but the use of a single drug, sodium oxybate, to control all symptoms of narcolepsy (including cataplexy) is gaining favor following a series of successful clinical trials [94; 96; 97; 98; 99; 100]. However, due to abuse potential, access to the drug is tightly restricted [42; 57].

If a CNS stimulant is prescribed in order to combat the effects of excessive daytime sleepiness, the most common are various amphetamines and methylphenidate [42; 93]. These agents can be effective in reducing daytime sleepiness and the occurrence of sleep attacks. Amphetamines (e.g., amphetamine, dextroamphetamine, methamphetamine) have been prescribed for narcolepsy since the 1930s and, at lower dosages, act primarily by causing dopamine (and noradrenaline) release [101]. They may be prescribed at 10–60 mg/day. However, amphetamine use is associated with a number of adverse effects, including headache, insomnia, irritability, nervousness, and palpitations, and less frequently, anorexia, hyperhidrosis, nausea, orofacial dyskinesia, and psychosis [93]. Abuse of prescribed amphetamines is rare among narcoleptics, but tolerance develops in one-third of patients. Due to these risks and the proven efficacy of newer drugs, amphetamines are no longer recommended as first- or second-line therapy. Methylphenidate has similar, though milder, adverse effects and a much shorter half-life [94]. It is also prescribed at 10–60 mg/day, but it is recommended only when modafinil is insufficiently active, when modafinil must be supplemented at a specific time of the day, or in situations where maximum alertness is required [42; 92].

Modafinil, a stimulant, was approved for use in the United States in 1998 and is the treatment of choice for narcolepsy when the most serious symptom is excessive daytime sleepiness due to its efficacy, limited adverse effects, and easiness of manipulation [42; 92]. To date, researchers have been unable to determine the exact mechanism(s) of action, but modafinil is known to increase the release of monoamines (e.g., dopamine, norepinephrine, histamine) from synapses [93; 102]. Therefore, the central histaminergic and dopaminergic systems are suspected to be involved. Unlike with classic CNS stimulants, the coadministration of a dopamine antagonist only partially weakens the effectiveness of modafinil, leading researchers to describe the drug as a wakefulness promoting agent [57; 103]. The starting dose is 200 mg, and the usual effective dose is 200–400 mg taken as a single morning dose or as a split dose (first in the morning and then around noon). However, evidence of benefit with a dose greater than 200 mg/day is lacking [57]. There is a low prevalence of common side effects, including headache (13%), nervousness (8%), nausea (5%), and rhinitis, all of which are typically mild [92; 94]. More serious side effects have been noted and are mainly allergic/inflammatory reactions, including hives, rash, and swelling. Other severe dermatologic reactions have occurred, such as drug rash with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN), prompting the FDA to issue a safety labeling change in 2007 [57]. There have been very few instances of DRESS, Stevens-Johnson syndrome, and TEN (less than 10 since 1998), and modafinil is considered a safe treatment for excessive daytime sleepiness.

For patients with excessive daytime sleepiness with poor nighttime sleep and cataplexy, the first-line treatment is sodium oxybate [92]. This drug, also known as gamma hydroxybutyrate (GHB), is a powerful sedative that has been burdened by the stigma as a party or "date-rape" drug and a performance-enhancing drug [94]. Misuse of the drug can be life-threatening, and steps should be taken to ensure no other sedatives (including alcohol), muscle relaxants, or respiratory depressants are taken concurrently and that sleep disordered breathing is not present or does not develop. Sodium oxybate is restricted and can only be prescribed by those enrolled in the Xyrem Patient Success Program and dispensed by the designated centralized pharmacy [57]. The initial dose is 4.5 g/night in two equal doses [57]. The first dose is taken sitting upright in bed just before sleep; the patient should lie down immediately after dose one; the second dose is taken 2.5 to 4 hours later. (An alarm may be necessary.) The dose can be increased by 1.5 g at two-week intervals up to a maximum dose of 9 g/night [57; 92]. Patients usually begin to improve after the first few nights, but the optimal response (even at the starting dose) can take up to 8 to 12 weeks. Adverse effects are common and include headache (9% to 37%), dizziness (8% to 37%), nausea (8% to 40%), vomiting (2% to 23%),

pain (9% to 20%), confusion (3% to 17%), sleep disorder (6% to 14%), somnolence (1% to 14%), abdominal pain (3% to 11%), enuresis (3% to 17%), and urinary incontinence (<1% to 14%, usually nocturnal) [57].

Antidepressants are considered second-line agents for cataplexy and are also an effective treatment for sleep paralysis and HHEs [92]. The most potent anticataplectic drugs are tricyclic antidepressants, especially clomipramine (10–75 mg). However, these agents have the disadvantage of anticholinergic side effects. SSRIs have fewer side effects but are slightly less active [92]. Venlafaxine, a norepinephrine/serotonin reuptake inhibitor, is widely prescribed despite a lack of published clinical evidence to support its use. The same paucity of data exists for norepinephrine reuptake inhibitors (e.g., reboxetine, atomoxetine) [92]. Other pharmacologic agents are no longer recommended for use based on either a lack of clinical efficacy data or on their undesirable adverse effects and safety profiles [92].

Caution should be given when treating patients with comorbid psychiatric disorders. Sodium oxybate should not be used in patients with depression. Instead, antidepressants should be prescribed along with a referral to a psychiatrist or mental health provider [92].

Behavioral Therapies

There are several lifestyle and dietary changes that may help reduce the symptoms and risks of narcolepsy, although there are no accepted behavioral treatments for cataplexy [92]. Behavior modification is useful as medications cannot ensure a consistent state of alertness in individuals with the disorder. Practicing strict sleep hygiene is important, and engaging in relaxation exercises or taking a bath before bedtime may offer a benefit [42]. Daytime napping has been shown to improve alertness and shorten reaction times [42]. Regular exercise (20 minutes/day, four to five hours before bedtime) can lead to better sleep and help prevent or reduce narcolepsy-related weight gain. Alcohol and caffeine should be avoided, especially at night.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The European Academy of Neurology, the European Sleep Research Society, and the European Narcolepsy Network recommend planned daytime naps to improve immediate subjective and objective sleepiness both in drug-naïve patients with narcolepsy and in those taking stimulant medication, at any age.

(https://onlinelibrary.wiley.com/doi/10.1111/ene.14888. Last accessed December 7, 2021.)

Level of Evidence: Expert Opinion/Consensus Statement

One of the major risks of narcolepsy is falling asleep while performing hazardous tasks (e.g., driving, operating machinery) or collapsing due to cataplexy at an ill-timed moment (e.g., while descending a stairway). Automobile accidents are 10 times more common in individuals with untreated narcoleptic symptoms, but when medication and behavioral therapies are being used, the accident rates are similar to healthy individuals [42]. Scheduled naps are recommended to reduce the likelihood of falling asleep unexpectedly. The Americans with Disabilities Act guarantees equal opportunity for narcoleptic students and workers, and reasonable adjustments to school and work schedules should be encouraged to accommodate periodic naps [42].

Support groups for narcolepsy are helpful for many patients. Overcoming feelings of isolation by connecting with other people with the disorder and lessening the sense of judgment by outsiders are important both for those who have just received a diagnosis and experienced patients alike. It may be difficult for individuals living in non-metropolitan areas to find a support group, and for these patients online groups can be useful. More information about narcolepsy support groups is available at https://www.narcolepsynetwork.org. The Narcolepsy Network offers meetings in several U.S. cities and hosts online support groups as well [104].

IDIOPATHIC HYPERSOMNIA

Idiopathic hypersomnia is a rare disorder, affecting approximately 50 people per million population [105]. However, there are many potential causes of daily, unrelenting hypersomnia, and the disorder is a consideration in the differential diagnosis of several other conditions and sleep disorders. Therefore, a brief discussion is warranted.

Idiopathic hypersomnia is characterized by excessive daytime sleepiness without cataplexy and is not better explained by another disorder [2]. Most hypersomniacs have extreme difficulty waking from sleep. If naps are taken, they are usually longer than those taken by individuals with narcolepsy, and many patients experience confusion or disorientation, called sleep drunkenness, upon waking [106]. Also unlike narcolepsy, most (though not all) patients wake from naps still feeling drowsy or unrefreshed. Irresistible urges to sleep (sleep attacks) are rare with this disorder, and cataplexy is not a feature [105; 106]. Narcoleptics typically have disturbed nighttime sleep, whereas patients with this disorder do not. Unusual or inappropriate behaviors (e.g., staring, acting intoxicated) may occur in patients who do not take daytime naps.

Diagnosis

There are many medical conditions that can cause hypersomnia, including Kleine-Levin syndrome, Parkinson disease, dementia, and post-traumatic stress disorder, all of which should be ruled out with a complete medical history, physical examination, and diagnostic workup. Standard sleep studies are used to confirm the diagnosis of idiopathic hypersomnia,

including MSLT and polysomnography. The absence of multiple SOREMPs (one or fewer) during MSLT and greater time spent in slow-wave sleep during polysomnography suggest idiopathic hypersomnia [105]. On the other hand, multiple SOREMPs (two or more) are indicative of narcolepsy.

Treatment

The same array of pharmacologic options used to treat excessive daytime sleepiness in narcolepsy may be prescribed for idiopathic hypersomnia, but the level of effectiveness is typically not replicated [105; 106]. Only half of patients treated report any improvement of symptoms. In 2021, the FDA expanded approval of oxybate salts (calcium, magnesium, potassium, and sodium) to include treatment of idiopathic hypersomnia [149]. It is the first and only medication approved for this indication; all other pharmacologic options are prescribed off label. Although sleep hygiene practices are usually not helpful for idiopathic hypersomnia patients, they should be discussed because there are virtually no risks or drawbacks [105]. Patients should be advised to avoid sedative drugs and alcohol.

OTHER HYPERSOMNIAS

Recurrent hypersomnia is characterized by periodic episodes of extreme somnolence accompanied by cognitive and behavioral disturbances lasting for days to weeks that punctuate an otherwise normal, healthy sleep pattern. During hypersomnia episodes, patients may sleep up to 20 hours per day (range: 10 hours to nearly 24 hours) [2; 107]. The average number of episodes is 2 per year, but it can occur up to 12 times per year. The most commonly known form of this disorder is Kleine-Levin syndrome, but there are other forms of recurrent hypersomnia with incomplete features of the syndrome, which may be associated with a medical disorder, psychologic disorder, or medication/substance use [2]. Kleine-Levin syndrome is exceptionally rare in the United States, with fewer than 1 case per million population, although some believe this is an underestimate [107]. The prevalence is greater in individuals of Jewish descent compared with the overall population [108]. The onset of Kleine-Levin syndrome usually occurs in adolescence and follows an infection, such as a cold or influenza.

All patients with recurrent hypersomnia have various forms of cognitive impairment and altered perception during episodes [108]. Cognitive symptoms include impaired speech (94%), difficulty with concentration (91%), and memory impairment (66%). Altered perception symptoms include dream-like state (81%), derealization (66%), and hypnagogic hallucinations (42%). Many patients experience other psychologic symptoms, including eating behavior disorders (95%), hypersexuality and disinhibition (53%), and depressed mood (53%) [108].

Recurring excessive sleepiness can occur during the premenstrual period in adolescent girls, referred to as menstrual-related hypersomnia, and is often controlled with birth-control pills [109]. This and other disorders that cause bouts of excessive sleepiness (e.g., encephalopathy, depression) should be differentiated from hypersomnia disorders.

Treatments include various stimulants, lithium, carbamazepine, and the antiparkinsonian drug amantadine, all of which have marginal efficacy [108; 109]. Hypersomnia episodes typically decrease in intensity and frequency within 8 to 12 years of onset, with eventual complete resolution common.

CIRCADIAN RHYTHM SLEEP-WAKE DISORDERS

Disorders that fall into the ICSD-3 category of circadian rhythm sleep-wake disorders are caused by alterations to the internal circadian timekeeping system or by environmental, physiologic, or behavioral factors that alter timing of sleep relative to an individual's circadian rhythm, leading to insomnia and/or excessive daytime sleepiness and impaired functioning [2]. Sleep timing that does not follow circadian rhythms will typically cause nonoptimal sleep. The ICSD-3 contains seven disorders of this type [2]:

- Delayed sleep-wake phase disorder
- Advanced sleep-wake phase disorder
- Irregular sleep-wake rhythm disorder
- Non-24-hour sleep-wake rhythm disorder
- Shift work disorder
- Jet lag disorder
- Circadian sleep-wake disorder not otherwise specified NOS

Most circadian rhythm sleep disorders are uncommon or occur overwhelmingly in specific populations (e.g., the non-24-hour sleep-wake rhythm type in blind individuals). Jet lag and shift work disorders are related to very specific sets of conditions. Medical conditions that may be responsible for circadian rhythm abnormalities include dementia, Parkinson disease, and hepatic encephalopathy [2]. Delayed sleep-wake phase disorder affects a significant number of adolescents and young adults.

DELAYED SLEEP-WAKE PHASE DISORDER

Delayed sleep-wake phase disorder is characterized by a habitually delayed sleep time (relative to socially acceptable or conventional sleep times) with difficulty falling asleep when others do [2]. The offset is usually more than two hours, but sleep is normal once initiated (though a late wake time is preferred if allowed). Daytime functioning is normal when individuals are allowed to sleep later, but dictated schedules cause deteriorated well-being. Depression or suicidal ideation may be the primary reason for adolescents' clinical presentation [2]. Patients with this disorder are definite "evening types."

The incidence of this disorder is unknown in the general population, but it is more common in adolescents and young adults (7% to 16%), with a mean onset of 20 years of age [2]. About 1 in 10 sleep clinic patients with chronic insomnia have a delayed sleep phase. Roughly 40% of patients with this disorder have a family member with the disorder [2].

Staying up late, with activity and indoor bright lights, can promote the disorder, as can a corresponding reduction in bright morning light [2]. Shift work, changes in schedules, and frequent travel across time zones can also precipitate the disorder. Attempts at retraining, using sleep hygiene and bright light therapy may work, but patients usually maintain a strong desire for "eveningness" despite intervention [2].

PARASOMNIAS

In the ICSD-3, parasomnias are divided into three categories: non-REM-related parasomnias (i.e., disorders of arousal from non-REM sleep), REM-related parasomnias, and other parasomnias [2]. Non-REM-related parasomnias consist of disorders of arousal, confusion arousals, sleepwalking, and sleep terrors, and sleep-related eating disorder; parasomnias usually associated with REM sleep consist of REM sleep behavior disorder, recurrent isolated sleep paralysis, and nightmare disorder. Other parasomnias consist of exploding head syndrome, sleep-related hallucinations, sleep enuresis, parasomnia due to a medical disorder, parasomnia due to a medication or substance, and parasomnia, unspecified [2].

SLEEPWALKING

Sleepwalking, or somnambulism, is a non-REM arousal disorder that causes individuals to walk or perform other activities while asleep. Activities may include sitting upright in bed, walking around inside/outside the house, moving furniture, getting dressed, preparing food, trying to "escape," jumping from windows, driving a car, and many others, though dangerous activities are rare [110; 111]. It is fairly common for sleepwalking children to engage in inappropriate behaviors, such as urinating in a closet or waste basket [2]. Accidents and falls may also occur, and people have even committed homicide or pseudosuicide while asleep. Patients can become violent when others attempt to awaken them from the sleepwalking episode, and most will be extremely confused if awakened and will not recall the events of the episode [110; 111].

It should be noted that sleep driving associated with z-drugs (e.g., zolpidem, zopiclone) and other psychiatric medications is unrelated to sleepwalking [112]. Sleep drivers will typically have some level of cognitive function (e.g., are responsive to police questioning) but will display poor balance and walking ability. Sleepwalkers, on the other hand, are perfectly able to balance while walking but have no ability to interact.

Sleepwalking typically occurs during non-REM sleep stage 3 (slow-wave sleep), which is more common early in the night (during the first-third of sleep) [110]. Episodes last an average of 10 minutes but range from a few minutes to more than 30 minutes. Patients usually return to bed before waking, but some may fall asleep in another location or awaken while sleepwalking [2]. Sleep talking may also be exhibited by these individuals, and sleep terrors may occur at other times. Sleepwalking episodes may occur frequently (several times per night, for several nights) or only rarely or when precipitating factors are present [2].

Epidemiology

The prevalence of sleepwalking ranges from 4% in adults to 17% in children [2]. The disorder may begin as soon as a child is able to walk, but the age of onset is usually between 4 and 8 years. The disorder is most common in children 5 to 12 years of age [2; 110]. A 2004 National Sleep Foundation poll found that sleepwalking a few nights per week occurs in 1% of preschoolers and 2% of school-age children [113]. Sleepwalking is more common in children with sleep enuresis (chronic bedwetting). Symptoms of sleepwalking disappear after adolescence in most patients; however, the disorder can occur at any age [2; 110]. Approximately one-third of cases develop after adolescence [2]. Girls and boys are affected equally in childhood, but the gender distribution in adults is not well defined [2]. One study of an adult population of sleepwalkers in Nigeria found prevalence roughly three times higher in men than in women [114].

Sleepwalking may occur in isolated cases, but there is a known genetic susceptibility and a familial pattern [2; 115]. The incidence in children is 60% when both parents have the disorder and 45% when one parent is affected. The incidence is 22% if neither parent has the disorder but when sleepwalking is familial (i.e., occurs in more distant relatives) [2]. A 2012 Stanford School of Medicine study found that the self-reported yearly incidence of sleepwalking was 3.6%, equating to about 8.5 million Americans [116]. According to the study, the lifetime prevalence of a sleepwalking episode was estimated at 29.2%, with 30.5% of participants reporting a family history of the disorder. Twin studies support the role of genetic susceptibility in at least 65% of cases [2].

Risk Factors

Although there is a strong heritable factor for sleepwalking, the pathology of sleepwalking is not known [2; 110]. Individuals who are predisposed to sleepwalking may become active sleepwalkers when priming factors exist and a precipitating factor triggers an episode [2; 115]. Priming factors deepen and increase slow-wave sleep and include anxiety, fatigue, fever, the premenstrual period, sleep deprivation, and physical or emotional stress. Alcohol use and certain medications may also be priming factors, but it is unclear if the many case reports of "sleepwalking" under the influence of substances are due to extreme intoxication or complex medication

interactions (or medication/psychopathologic interactions) [2; 110; 115]. Precipitating factors, or triggers, identified in primed individuals in sleep laboratories include light, noise, periodic leg movements, sleep disordered breathing, and touch.

Certain mental disorders (e.g., obsessive-compulsive disorder) and medical conditions (e.g., organic brain syndrome, partial complex seizures) are associated with sleepwalking, as is obstructive sleep apnea [2; 110; 116]. Medication-related sleepwalking may occur, most commonly in individuals with a complex medical and psychiatric history associated with multiple medications [115]. The 2012 study found a higher risk of frequent sleepwalking episodes (two or more times/month) with obstructive sleep apnea syndrome (odds ratio [OR]: 3.9), obsessive-compulsive disorder (OR: 3.9), alcohol abuse/dependence (OR: 3.5), major depressive disorder (OR: 3.5), circadian rhythm sleep disorder (OR: 3.4), SSRI antidepressant use (OR: 3.0), over-the-counter sleep aid use (OR: 2.5), and insomnia disorder (OR: 2.1) [116].

Diagnosis

Steps should be taken to ensure that sleepwalking is not the result of a medication side effect or an underlying medical or psychiatric condition. Specific medications and their dosages should be reviewed. In cases of pediatric sleepwalking, parents or caretakers will have witnessed one or more behaviors associated with the disorder, including [110; 111]:

- Aggressive behavior when aroused (rare)
- The appearance of being awake while still asleep
- Open eyes during sleep, with a blank look on the face
- Confusion or disorientation when roused
- Performance of detailed activities during sleep
- No memory of the sleepwalking episode
- Sleep-talking and nonsensical verbalizations

Adult patients with no history of the disorder may similarly present with no recollection of any episode of sleepwalking or associated behaviors, which may have instead been witnessed by another person. Sleep studies and other tests and procedures are typically not needed to confirm a diagnosis in patients with known good health [2; 110]. However, testing to rule out other medical conditions (e.g., partial complex seizures, obstructive sleep apnea) in patients with a limited medical history is recommended.

Treatment

There is no cure or specific treatment for sleepwalking [110; 113]. As a first step in the management of sleepwalking, conditions or medications that may cause somnambulism should be identified and treated or discontinued, which may eliminate or greatly reduce sleepwalking episodes. For patients with sleepwalking as the primary diagnosis, identifying the priming and precipitating factor(s) is a cornerstone of management. Patients (or parents) should be instructed to keep a journal that includes daily activities, level of daytime sleepiness, total hours of sleep, and any illnesses or triggers of stress or anxiety to help to determine possible triggers, though dedication to observation and journaling lessens and more omissions occur over time [117].

Again, there is no high-quality evidence to support any specific sleepwalking treatment [113; 118]. A tailored approach to therapy, including improvements in sleep hygiene, should be made on a patient-by-patient basis. Although medication is not usually required and is not recommended as a first-line therapy, sedative-hypnotics, tricyclic antidepressants, or SSRIs may be prescribed if sleepwalking interferes significantly with the patient's or the family's quality of life (e.g., excessive daytime sleepiness, high risk of injury, unusual symptoms, inappropriate behaviors causing family distress) [110; 113]. However, the usefulness of these medications is not certain [119; 120]. Care must be taken when prescribing tricyclic antidepressants, as they have many serious side effects (especially in children) and can exacerbate sleepwalking [121]. Benzodiazepines (e.g., clonazepam, diazepam) were initially prescribed for sleepwalking, with only limited benefit [119; 120]. A 2021 review reports that benzodiazepines are effective at controlling sleepwalking [122]. One study of individuals with either isolated sleepwalking or sleepwalking related to psychiatric conditions or obstructive sleep apnea found that benzodiazepines and psychiatric medications were not effective in reducing sleepwalking episodes. Nasal CPAP therapy for participants with obstructive sleep apnea eliminated sleepwalking in all individuals who remained compliant throughout each of the follow-up periods [120].

Hypnosis has been used as a low-cost, safe therapy for various parasomnias, including sleepwalking [113; 123]. One small-scale study (27 participants) conducted by Hurwitz and colleagues showed a 74% success rate for long-term reduction of sleepwalking and night terror episodes ("much" or "very much" improvement on self-report) following one to six office visits and continued with at-home self-hypnotic exercises [124]. A five-year follow-up study of 36 parasomnia patients (modeled on the Hurwitz study) found a 45.4% success rate after 1 month (symptom free or "much improved"), which diminished slightly to 42.2% at 18 months and 40.5% at 5 years [125]. In this study, participants underwent one or two 50-minute hypnosis sessions, described as "deep physical relaxation but with retention of an active and focused mind, so possible new thoughts could be evaluated and incorporated into the hypnotized person's thinking" [125].

One behavioral approach, anticipatory awakenings, can be effective in reducing sleepwalking episodes. This method requires parents or caretakers to wake the patient three hours into the night and 15 minutes before the usual sleepwalking time. The patient is kept awake for 30 minutes and then may return to sleep. Anecdotal reports have found this intervention to be successful; however, it requires a significant commitment on the part of those involved [121; 126].

Another key to treatment is the maintenance of a safe living environment. Patient/parent education should cover precautions to be taken, including [113; 121]:

- Locking windows and doors in a way that allows for safe emergency exit
- Installing door alarms on all doors that lead outside or to a basement or attic
- Securing all potentially dangerous objects or items (e.g., tripping hazards, sharp objects, chemicals, medications, knives, guns)
- Moving the patient's bedroom to the ground floor (if possible)
- Covering windows to block out light

SLEEP-RELATED MOVEMENT DISORDERS

The ICSD-3 includes 10 sleep-related movement disorder diagnoses: restless legs syndrome; periodic limb movement disorder (PLMD); sleep-related leg cramps; sleep-related bruxism; sleep-related rhythmic movement disorder; benign sleep myoclonus of infancy; propriospinal myoclonus at sleep onset; sleep-related movement disorder due to a medical disorder; sleep-related movement disorder due to a drug or substance; and; sleep-related movement disorder, unspecified [2].

RESTLESS LEGS SYNDROME AND PERIODIC LIMB MOVEMENT DISORDER

Although restless legs syndrome and PLMD are two distinct disorders, they are often discussed together, as they have overlapping features. PLMD is also comorbid in most (85% to 90%) patients with restless legs syndrome [2; 127].

Restless legs syndrome, also known as Willis-Ekbom disease, is a neurologic sleep disorder characterized by disagreeable leg sensations that worsen when individuals are at rest (e.g., when seated) and/or at night before bedtime [2]. There is an accompanying urge to move the legs to relieve the unpleasant sensations, which are described as aching, bubbling, creeping, crawling, pulling, searing, and/or tingling; walking, stretching, or shaking usually provides relief [128]. The area between the ankle and the knee is most often affected (usually bilaterally), but the thighs, feet, and, to a lesser extent, the arms may also be affected [2]. Pathologic changes in efficiency of central dopamine neurotransmission are thought to cause the disorder, based on the observation that restless legs syndrome symptoms are relieved by the use of dopaminergic drugs [127]. The secondary (non-idiopathic) form of restless legs syndrome can be caused by a variety of medical conditions. Iron deficiency and uremia are common causes; others include chronic kidney disease, cobalamin (vitamin B12) deficiency, folate deficiency, diabetes, fibromyalgia, Parkinson disease, peripheral neuropathy, pregnancy, radiculopathy, rheumatoid arthritis, Sjögren syndrome, use of certain drugs (e.g., caffeine, calcium channel blockers, lithium, neuroleptics), and withdrawal from sedatives [128; 129].

Troubling and painful leg sensations that cause an irresistible urge to move initially keep patients from being able to sleep, and the discomfort is often so disrupting that patients awaken several hours after falling asleep. As such, restless legs syndrome is a significant cause of (secondary) insomnia. Periodic limb movements during sleep are very common in patients with restless legs syndrome, and involuntary limb movements occur in many patients with restless legs syndrome while awake [2]. Involuntary limb movements while awake are much less common among patients with PLMD alone.

PLMD is characterized by episodes of repetitive, stereotyped leg movements during stage 1 and stage 2 sleep, consisting of extension of the big toe in combination with partial flexion of the ankle, knee, and sometimes hip [2; 127]. The legs typically remain still during non-REM stages 3 and 4 and during REM sleep. Episodes prevail during the first half of the night and diminish progressively [129]. Intermittent flexion at the elbow may also be seen in some patients.

Some patients may not be roused by the movement episodes and only complain of excessive daytime sleepiness. However, the typical presentation is with frequent awakenings and poor sleep quality (i.e., insomnia). Bed partners' sleep is often disturbed by the movements. As with restless legs syndrome, this disorder is also thought to be caused by altered dopamine neurotransmission (based on the efficacy data of dopaminergic drugs) but can also be caused by a medical condition [127]. Certain medications can cause periodic limb movements during sleep, including tricyclic antidepressants (e.g., amitriptyline), neuroleptics and other antidopaminergic agents (e.g., haloperidol), and dopaminergic agents (e.g., carbidopa, which may be used in the treatment of PLMD).

Epidemiology

Approximately 5% to 15% of the adult U.S. population is affected by restless legs syndrome, and women are affected twice as often as men [2; 130]. The disorder is more common in certain groups, including pregnant women (11%), uremic patients (15% to 20%), and patients with rheumatoid arthritis (up to 30%). In general, restless legs syndrome is associated with advancing age; however, the age of onset is younger than 20 years in one-quarter of patients. Among children 8 to 11 years of age and adolescents 12 to 17 years of age, the prevalence is 1.9% and 2.0%, respectively [109]. Restless legs syndrome symptoms usually appear after the 20th week when associated with pregnancy [2].

The exact incidence of PLMD alone is unknown in adults [2]. However, it is very uncommon in children and is more prevalent after middle age, with approximately 44% of adults 65 years of age or older found to have symptoms of the disorder [2; 129]. It is unclear if the prevalence among older adults differentiates symptoms indicative of idiopathic

JOHNS HOPKINS RESTLESS LEGS SYNDROME SEVERITY SCALE	
Timing of Symptoms	**Score**
No symptoms	0 (never)
Symptoms less than daily or almost daily	0.5 (infrequent)
At bedtime and/or during the sleep period. Symptoms may occur within 60 minutes before the usual bedtime or simply at the time of going to bed or during the night after in bed.	1 (mild)
Evening, after 6 p.m. Symptoms may occur anytime between 6 p.m. and the usual bedtime. (The definition of evening may need to be adjusted for patients who routinely have much later bedtimes.)	2 (moderate)
Afternoon, before 6 p.m. Symptoms may start in the afternoon and persist into the evening or night.	3 (severe)
Before noon. Symptoms may start in the morning or they may present virtually all day. There is usually a "protected period" in the mid-morning (8—10 a.m.) with few if any symptoms.	4 (very severe)
Source: Reprinted from Allen RP, Earley CJ. Validation of the Johns Hopkins restless legs severity scale. Sleep Med. 2001;2(3):239-242, with permission from Elsevier.	*Table 5*

PLMD and limb movements related to other conditions, but some questions have been raised as to whether PLMD is a true sleep disorder based on the high prevalence in this population [129].

Risk Factors

There is a strong heritable risk factor for restless legs syndrome [128; 130]. One study found that more than 70% of pediatric patients with restless legs syndrome had at least one parent with the disorder [109]. As noted, restless legs syndrome is more common in women, but race does not appear to be a factor [2]. Overall, prevalence and incidence have not been well defined [109; 127].

Medical or psychiatric conditions and certain medications have been associated with an increased incidence of restless legs syndrome and/or PLMD. Children with attention deficit hyperactivity disorder are more likely to have both restless legs syndrome and PLMD. Uremia and other metabolic disorders are known to cause periodic limb movements during sleep [2]. Monoamine oxidase inhibitors and tricyclic antidepressants can cause or worsen the disorder, as can withdrawal from certain drugs, including anticonvulsants, benzodiazepines, barbiturates, and other hypnotic agents. PLMD may be associated with an underlying arousal disorder [128].

Diagnosis

The history and physical examination should focus on differentiating restless legs syndrome from other conditions with shared features, including akathisia, anxiety disorders, chronic myelopathy, erythromelalgia, leg compartment syndromes, muscular pain fasciculation syndromes, myokymia, and peripheral neuropathy [2]. Subclinical hypopneas can also trigger limb movements. Iron-deficiency anemia, caffeinism, and uremia should also be considered as possible causes of secondary restless legs syndrome. The use of and withdrawal from high-risk medications should also be identified from the medical history. All conditions known to cause the symptoms indicative of the disorder should be ruled out, and serology should be obtained (e.g., cobalamin, creatinine, ferritin, folate, iron, urea) [127; 129; 130]. Additional serology and electrodiagnostic testing may be considered if peripheral neuropathy is suspected. The presence of periodic limb movements during sleep is a strong indication of restless legs syndrome. Several instruments are available to measure restless legs syndrome severity, including the Johns Hopkins Restless Legs Syndrome Severity Scale (***Table 5***) and the Restless Legs Syndrome Quality of Life Instrument (RLS-QLI) [131]. The RLS-QLI consists of 17 items that assess the patient's social function, daily function, sleep quality, and emotional well-being, while the Johns Hopkins measure focuses on timing of symptoms [132; 133].

Sleep studies are not typically needed for a diagnosis of restless legs syndrome to be made; however, periodic limb movements during sleep may be confirmed using polysomnography, if necessary [2; 127]. Polysomnographic features of PLMD are recorded using bilateral anterior tibialis EMG. Patterns of movement include repetitive contractions (four or more, with a duration of 0.5 to 5 seconds)—typically a leg jerk, followed by a short interval (milliseconds) and a tonic contraction—spaced apart by 20 to 40 seconds of relaxed muscle tone [2]. Both legs are involved in the majority of patients, but there may be inconsistent and random alternation between the left and right limbs or a unilateral,

predominant pattern. The periodic limb movement arousal index measures the number of limb movements associated with EEG arousals per hour. Mild PLMD is defined as 5 to 25 movements per hour, moderate as 25 to 50 per hour, and severe as more than 50 movements per hour or more than 25 movements associated with arousals per hour [129].

Treatment

Anticonvulsants, dopamine agonists, tranquilizers, and opioid narcotics are used to manage symptoms of restless legs syndrome, and iron supplements are used when indicated [127; 128]. Dopamine agonists considered effective for restless legs syndrome management include pramipexole and ropinirole, but rotigotine is recommended for long-term therapy [128; 134]. These and other antiparkinsonian drugs are also first-line therapies for PLMD and may improve sleep in patients with both disorders. The anticonvulsants gabapentin and pregabalin reduce movement symptoms and neuropathic pain in patients with either restless legs syndrome or PLMD and may also help to improve sleep; however, use of these medications for restless legs syndrome and PLMD is off-label [57; 128]. Gabapentin enacarbil is on-label and is preferred over gabapentin for long-term treatment [57; 134]. Other treatments for these sleep disorders include stress management, muscle relaxation exercises, and sleep hygiene.

The initial dosage of pramipexole (immediate-release) is 0.125 mg once daily, two to three hours before bedtime, but higher doses (up to 0.5 mg) are typically required in order to be effective [57]. The maximum recommended dose is 0.5 mg, but doses up to 2 mg daily are occasionally used. The most frequent side effects are nausea (11% to 27%), particularly early in treatment, and headache (16%) [57]. There is no evidence that doses higher than 0.5 mg/day offer benefit [135].

The initial dose of ropinirole (immediate-release) is 0.25 mg taken one to three hours before bedtime; the dose may be increased to 0.5 mg after two days, to 1 mg after one week, and to a maximum dose of 4 mg at week 7. Common adverse effects include dizziness (6% to 40%), fatigue (8% to 11%), nausea (40% to 60%), somnolence (11% to 40%), syncope (1% to 12%), and viral infection (11%) [57].

The American Academy of Sleep Medicine has identified pramipexole and ropinirole as the agents with the highest level of evidence supporting their use in the treatment of patients with restless legs syndrome.

(https://aasm.org/resources/practiceparameters/updateto.pdf. Last accessed December 7, 2021.)

Strength of Recommendation/Level of Evidence: Standard (High or moderate evidence that benefits clearly outweigh harm/burden)

The rotigotine (transdermal patch) initial dose is 1 mg/24 hours (one patch per day). The daily dose may be increased by 1 mg/24 hours each week, to a maximum daily dose of 3 mg/24 hours [57]. Dose-related application site reactions are common (21% to 46%), as are gastrointestinal complications such as nausea (15% to 48%) and vomiting (2% to 20%), and CNS reactions (e.g., somnolence, dizziness, headache, fatigue, orthostatic hypotension, hallucinations) [57]. Therefore, an extended low-dose trial is recommended.

Higher doses of gabapentin (2,000–2,400 mg daily) have been found to be significantly more effective than placebo in reducing moderate-to-severe restless legs syndrome symptoms, but higher doses are also associated with a high prevalence of adverse effects (e.g., dizziness, fatigue, nausea, pain, weakness) [57; 136]. The recommended initial dose for restless legs syndrome treatment (off-label) is 300 mg taken two hours before bedtime; the dose may be titrated every two weeks, until desired response is achieved, to a maximum dose of 1,800 mg [57]. (Dosages of up to 3,600 mg have been tolerated in short-term studies but are not recommended.) A combination of lower-dose gabapentin (300–1,000 mg daily) and ropinirole (0.25–1.5 mg daily) is also effective for treating restless legs syndrome and is associated with a lower incidence of adverse effects than high-dose gabapentin alone [136].

Gabapentin enacarbil is FDA-approved for the treatment of restless legs syndrome and is preferred over gabapentin due to longer duration of action and improved absorption [57; 134; 137]. The dosage is 300-600 mg once daily at approximately 5 p.m. Worsening side effects are seen at higher doses, and no benefit is reported at a dose of 1,200 mg compared with 600 mg [57]. Adverse effects (at a 600-mg daily dose) include dizziness (13% to 17%), headache (10% to 12%), and somnolence (20%), and a low rate of gastrointestinal effects are also observed (e.g., nausea, 6% to 8%) [57]. Pooled analysis of long-term use of gabapentin and other antiepileptic drugs has validated concerns regarding suicidal ideation and behavior (0.43%) compared with placebo (0.24%) [57]. Human data regarding pancreatic cancer risk have yet to be compiled, although gabapentin is associated with pancreatic adenocarcinoma in rats [57; 137].

Multiple studies have shown that pregabalin is effective for managing sensory and motor symptoms of restless legs syndrome and has a low rate of mild adverse effects across a wide dosage range [138; 139]. A reduction of periodic limb movements and sleep architecture improvements (e.g., increase in slow-wave sleep, decrease in waking after sleep onset and during sleep stages 1 and 2) were noted. In one study, the mean effective dose for pregabalin was approximately 350 mg/day, but in another study, a dose of 125 mg/day was shown to be effective in 90% of participants [138; 139]. Pregabalin is usually taken in divided doses, either two or three times a day [57]. Dizziness (3% to 45%) and somnolence (17% to 26%) are the most frequent adverse effects [57; 138].

Lifestyle Modifications and Alternative Therapies

Stress reduction, muscle relaxation techniques, and physical activity are important components of a restless legs syndrome management strategy, along with improved nutrition, proper sleep hygiene, and elimination of caffeine and alcohol intake [128; 129; 130; 131]. Supplementation with specific vitamins and minerals known to support the nervous system and improve blood circulation (e.g., vitamins B12, C, D, and E; glucosamine; magnesium; zinc) may be considered for patients with inadequate nutritional intake, but little research exists apart from small studies showing some degree of symptom reduction with supplementation with vitamins B and E [131]. Other alternative therapies with little or no scientific support include acupuncture, meditation, and prayer.

Moderate aerobic exercise and lower-body resistance training are recommended to both assist in the relief of psychologic stress and lessen the severity of symptoms [128]. Endorphin release, dopamine production, and increased blood flow to leg muscles are believed to mediate symptoms [131]. Massage, warm baths, and heating pads may also be used to relieve and/or prevent restless legs syndrome symptoms, though there is a lack of strong efficacy data for these therapies [130]. Case studies have shown a positive effect with massage (and a return of symptoms after cessation of massage therapy regimens), but the mechanisms involved are unclear [131]. Theories include improved blood circulation, dopamine release, counterstimulation of the cerebral cortex, and modulated thalamic neural activity as a response to tactile and temperature stimulus. Pulsed pneumatic compression devices have also been shown to reduce symptom severity; the proposed beneficial mechanisms are similar to those of massage [131]. Near-infrared light therapy has also successfully reduced restless legs syndrome symptom severity in small-scale studies [140].

There is a strong placebo effect in restless legs syndrome therapy [131]. A 2008 meta-analysis of 36 clinical trials found that one-third of patients had a significant improvement while receiving placebo medications [141]. In 24 of the trials, 40% of participants had a placebo response. However, this level of response was based on a reduction in the International Restless Legs Severity Scale score alone, and the placebo response was only moderate for other measures (e.g., daytime functioning, other restless legs syndrome measures). The placebo effect was found to be small for PLMD therapy [141].

In 2014, the FDA cleared the first device to improve sleep quality in patients with restless legs syndrome [142]. The device, marketed as Relaxis, consists of a vibrating pad that provides counterstimulation to a patient's legs as he or she sleeps. The manufacturer cautions that this device should not be used on patients who have had deep venous thrombosis in either leg in the six months prior to the initiation of therapy.

DIAGNOSING AND TREATING SLEEP DISORDERS WITH THE HELP 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 the treatment and management of sleep disorders, 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. (In many cases, the terms "interpreting" and "translating" are used interchangeably, but interpreting is specifically associated with oral communication while translating refers to written text.) While this may be easier said than done, due to institutional and/or patient barriers, the U.S. Department of Health and Human Services Office for Civil Rights has stated that denying adequate interpreter services to patients with limited English proficiency is a form of discrimination and that insufficient use of professional interpreters and inappropriate reliance on ad hoc interpreters may compromise patient care [143].

Depending upon the patient's language, an interpreter may be difficult to locate. Or, an organization may not have the funds to bring in an interpreter. Many view interpreters merely as neutral individuals who communicate information back and forth. However, another perspective is that the interpreter is an active agent, negotiating between two cultures and assisting in promoting culturally competent communication and practice [144]. In this more active role, the interpreter's behavior also is influenced by a host of cultural variables, such as gender, class, religion, educational differences, and power/authority perceptions of the patient [144]. Consequently, an intricate, triangular relationship develops between all three parties. Another factor affecting the communication process is that many interpreters are not adequately trained in the art of interpretation in mental health and general health settings, as there are many technical and unfamiliar terms. An ideal interpreter goes beyond being merely proficient in the needed language/dialect [145]. Interpreters who are professionally trained have covered aspects of ethics, impartiality, accuracy, and completeness [146]. They also are well-versed in interpreting both the overt and latent content of information without changing any meanings and without interjecting their own biases and opinions [146]. Furthermore, knowledge about cross-cultural communication and all the subtle nuances of the dynamics of communicating in a mental health or general health setting is vital [145].

On the patients' side, they may be wary about using interpreters for a host of reasons. They may find it difficult to express themselves through an interpreter [147]. If an interpreter is from the same community as the patient, the client/patient may have concerns about sharing private information with an individual who is known in the community and the extent to which the information disclosed would remain confidential. In some cases, raising the issue of obtaining an interpreter causes the client/patient to feel insulted that their language proficiency has been questioned. Finally, if an interpreter is from a conflicting ethnic group, the patient may refuse having interpreter services. The ideal situation is to have a well-trained interpreter who is familiar with health and mental health concepts.

If an interpreter is required, the practitioner should acknowledge that he/she is more than a body serving as a vehicle to transmit information verbatim from one party to another [147]. Instead, the interpreter should be regarded as part of a collaborative team, bringing to the table a specific set of skills and expertise [147]. Several important guidelines should be adhered to in order to foster a beneficial working relationship and a positive atmosphere.

A briefing time between the practitioner and interpreter held prior to the meeting with the client/patient is crucial. The interpreter should understand the goal of the session, issues that will be discussed, specific terminology that may be used to allow for advance preparation, preferred translation formats, and sensitive topics that might arise [145; 147; 148]. It is important for the client/patient, interpreter, and practitioner to be seated in such a way that the practitioner can see both the interpreter and client/patient. Some experts recommend that the interpreter sit next to the client/patient, with both parties facing the practitioner [146].

The practitioner should always address the client/patient directly. For example, the practitioner should query the client/patient, "How do you feel?" versus asking the interpreter, "How does she feel?" [146]. The practitioner should also always refer to the client/patient as "Mr./Mrs. D," rather than "he" or "she" [147]. This avoids objectifying the client/patient.

At the start of the session, the practitioner should clearly identify his/her role and the interpreter's role [147]. This will prevent the client/patient from developing a primary relationship or alliance with the interpreter, turning to the interpreter as the one who sets the intervention [145]. The practitioner also should be attuned to the age, gender, class, and/or ethnic differences between the client/patient and the interpreter [147]. For example, if the client/patient is an older Asian male immigrant, and the interpreter is a young, Asian female, the practitioner should be sensitive to whether the client/patient is uncomfortable, given the fact he may be more accustomed to patriarchal authority structures. At the conclusion of the session, it is advisable to have a debriefing time between the practitioner and the interpreter to review the session [145; 147; 148].

In this multicultural landscape, interpreters are a valuable resource to help bridge the communication and cultural gap between clients/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 diagnostic procedures, treatment options, and medication/treatment measures are being provided, the use of an interpreter should be considered.

CONCLUSION

Consistent and refreshing sleep is vital to health and an overall sense of wellness. However, nearly 25% of the U.S. population is troubled by a sleep disorder, many of which remain undiagnosed or undertreated, leading to a sleep deficit that can be difficult or impossible to repay. While most forms of disordered sleep are not immediately life-threatening, they can cause considerable distress, including accidental injury, depression, fatigue, and substance abuse. Most patients with a sleep disorder initially present to their primary care provider or other non-specialist, and appropriate identification and treatment or referral are important in this setting. This is especially true for the handful of sleep disorders that cause the majority of morbidity and mortality, including obstructive sleep apnea, narcolepsy, and insomnia. Increased understanding and adherence to best practices can improve patients' quality of life and help prevent associated complications.

Customer Information/Answer Sheet/Evaluation insert located between pages 96–97.

COURSE TEST - #98883 SLEEP DISORDERS

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

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

This 10 credit activity must be completed by December 31, 2024.

1. The primary zeitgeber in humans is
A) *body temperature.*
B) *the light-dark cycle.*
C) *hormone production.*
D) *the earth's magnetic field.*

2. In a healthy adult, most sleep time is spent in
A) *stage 1.*
B) *stage 2.*
C) *stages 3.*
D) *rapid eye movement (REM) sleep.*

3. According to the American Academy of Sleep Medicine, approximately how many unique sleep disorders are there?
A) *20*
B) *40*
C) *60*
D) *80*

4. Which of the following is NOT one of the three conditions used to identify insomnia?
A) *Chronic sleep difficulty*
B) *Poor sleep environment*
C) *Ample time and opportunity for sleep*
D) *Daytime dysfunction associated with sleep deficit*

5. The practice of sleep hygiene involves all of the following, EXCEPT:
A) *Using the bed only for sleep and sex*
B) *Eating large, heavy meals to induce sleep*
C) *Not taking or rarely taking daytime naps*
D) *Avoiding alcohol, caffeine, and nicotine four to six hours before bedtime*

6. When prescribing sedative-hypnotics for patients with insomnia, clinicians should
A) *use the lowest effective dose.*
B) *prescribe for longer durations (e.g., three or more weeks).*
C) *discontinue rapidly in order to avoid the development of resistance.*
D) *reserve use for patients with histories of substance abuse, acute cerebrovascular accident, myasthenia gravis, or respiratory impairment.*

7. Central sleep apnea due to Cheyne-Stokes breathing is primarily associated with
A) *overweight and obesity.*
B) *pulmonary hypertension.*
C) *congestive heart failure and stroke.*
D) *premature birth and low birth weight.*

8. An apnea-hypopnea index (AHI) scale score of 7 would indicate
A) *normal nighttime breathing.*
B) *mild obstructive sleep apnea.*
C) *moderate obstructive sleep apnea.*
D) *severe obstructive sleep apnea.*

9. The only statistically significant risk factor for obstructive sleep apnea is
A) *smoking.*
B) *alcohol consumption.*
C) *overweight and obesity.*
D) *polycystic ovary syndrome.*

10. The preferred method of objective sleep testing for patients with obstructive sleep apnea is
A) *electroencephalogram.*
B) *in-laboratory polysomnography.*
C) *home testing with a portable monitor.*
D) *body position monitoring during sleep.*

Test questions continue on next page ➔

11. Continuous positive airway pressure (CPAP) therapy is recommended for patients with
- A) *severe obstructive sleep apnea.*
- B) *moderate obstructive sleep apnea.*
- C) *mild obstructive sleep apnea who have failed to improve with behavior modification.*
- D) *All of the above*

12. Primary surgical treatment is indicated for patients with obstructive sleep apnea who have
- A) *gross anatomic abnormalities that are correctable.*
- B) *failed to improve with PAP therapy or with an oral appliance.*
- C) *a body mass index of 30 with no history of lifestyle changes.*
- D) *a gross obstruction that is deemed likely to interfere with the placement, effectiveness, or tolerance of either oral appliances or PAP.*

13. Sleep attacks associated with narcolepsy usually occur
- A) *at night.*
- B) *during periods of intense concentration.*
- C) *at a moment of extreme excitement or agitation.*
- D) *during activities or situations in which sleepiness is common.*

14. The age of onset of narcolepsy is usually
- A) *before 5 years.*
- B) *between 7 and 25 years.*
- C) *between 30 and 40 years.*
- D) *after 65 years.*

15. The treatment of choice for narcolepsy when the most serious symptom is excessive daytime sleepiness is
- A) *modafinil.*
- B) *amphetamines.*
- C) *methylphenidate.*
- D) *selective serotonin reuptake inhibitors (SSRIs).*

16. The initial recommended dose of sodium oxybate for patients with narcolepsy, excessive daytime sleepiness with poor nighttime sleep, and cataplexy is
- A) *1.5 g/week.*
- B) *a single 200-mg morning dose.*
- C) *4.5 g/night in two divided doses.*
- D) *9 g/night in two divided doses.*

17. Which of the following polysomnography findings is indicative of idiopathic hypersomnia?
- A) *Greater time spent in REM sleep*
- B) *Greater time spent in slow-wave sleep*
- C) *Sleep spindles and associated K-complexes*
- D) *Progressively decreasing theta-range brain activity*

18. One factor that may precipitate delayed sleep-wake phase disorder is
- A) *early wake time.*
- B) *anxiety regarding sleep cues.*
- C) *frequent travel across time zones.*
- D) *adherence to an excessively strict sleep schedule.*

19. Sleepwalking typically occurs during
- A) *REM sleep.*
- B) *stage 1 sleep.*
- C) *stage 2 sleep.*
- D) *non-REM stage 3 sleep.*

20. In patients with restless legs syndrome, the area most often affected is the
- A) *feet.*
- B) *lateral hip.*
- C) *upper thighs.*
- D) *area between the ankle and the knee.*

Be sure to transfer your answers to the Answer Sheet insert located between pages 96–97.
PLEASE NOTE: Your postmark or facsimile date will be used as your test completion date.

Men's Health Issues

Special Approvals

This course meets the requirements for two hours of cultural competency education and one hour of LGBTQ awareness education.

This course meets the requirements for seven hours of geriatric medicine education for California physicians.

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

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

Audience

This course is designed for physicians, physician assistants, nurses, and behavioral health professionals seeking to enhance their knowledge of issues related to men's health.

Course Objective

The purpose of this course is to provide health and mental healthcare professionals with necessary information regarding conditions and health issues that affect men in order to facilitate more effective diagnosis, treatment, and care. As male-specific factors influence the provision and compliance to therapy, tools to ensure effective patient education for men are provided to increase the likelihood of positive outcomes.

Learning Objectives

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

1. Identify diseases that are more prevalent among men than among women.
2. Describe the health implications of male gender identity and identify strategies to improve communication with male patients.
3. Explain the diagnosis and treatment of benign prostate conditions and prostate cancer.
4. Apply guideline recommendations for prostate cancer screening.
5. Describe treatment options and assist patients in selecting a management strategy for localized prostate cancer.
6. Distinguish among benign testicular conditions.
7. Discuss the diagnosis and treatment options for testicular cancer.
8. Discuss the differences between male and female breast cancer.
9. Discuss diagnosis and treatment options, and assist patients in selecting a treatment strategy for sexual dysfunction (premature ejaculation and erectile dysfunction).
10. Devise a strategy for diagnostic testing and treatment of late-onset hypogonadism.
11. List factors affecting male infertility.
12. Promote patient education and disease prevention, implement effective screening, and select guideline-appropriate treatment of sexually transmitted infections.
13. Identify issues of particular concern for men who have sex with men.
14. Discuss the effects of substance misuse, depression, and stress/anger on the physical and psychosocial well-being of men.
15. Discuss the importance of educating men about the need for screening, routine health maintenance, and healthy lifestyle.

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.

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

Faculty Disclosure

Contributing faculty, Lori L. Alexander, MTPW, ELS, MWC, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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

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Division Planner/Director Disclosure

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

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Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 15 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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Successful completion of this CME activity, which includes participation in the evaluation component, earns credit toward the Lifelong Learning requirement(s) for the American Board of Ophthalmology's Continuing Certification program. It is the CME activity provider's responsibility to submit learner completion information to ACCME for the purpose of granting 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.

Special Approvals

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

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INTRODUCTION

There are many reasons to be concerned about health issues that are unique to or more common in men. In 1900, women outlived men by an average of two years; that gap widened to seven years in 1970 through 1990 [1]. Advances in diagnosis and treatment, as well as heightened awareness of disparities in men's and women's health, led to a narrowing of the gap to slightly less than five years in 2014 [1]. Still of concern, however, is the high number of men's deaths that are potentially avoidable. Many factors contribute to the disparity in mortality and morbidity between men and women, but the factor thought to have the most significant impact on the health of men relates to male gender identity, including a tendency for risky behavior [2; 3; 4; 5].

The concept of men's health was established to focus on the high rates of morbidity and mortality. Thus, men's health encompasses both male-specific conditions, such as those related to the prostate, as well as diseases that affect men at a higher rate compared with women. A discussion of all diseases that affect men is beyond the scope of this course. However, the leading causes of death among men are presented and discussed in the context of how they compare with the causes of death in women.

Among the male-specific conditions addressed are prostate disease (e.g., prostatitis, benign prostatic hypertrophy [BPH], cancer), testicular conditions (e.g., testicular torsion, epididymitis, varicocele, cancer), premature ejaculation, erectile dysfunction, late-onset hypogonadism, infertility, and sexually transmitted infections (STIs). Prostate cancer is discussed in considerable detail. Prostate screening and treatment have been controversial issues in health care, and the most recent recommendations for how to discuss screening and treatment options are included. Also provided are brief overviews of male breast cancer, a rare disease but one that is rising in prevalence, and health issues of specific concern for men who have sex with men (MSM), a growing population seen in the primary care setting.

The psychosocial well-being of men is integral to overall health. The link between anger and stress and disease is mentioned, as is the major role of substance misuse in mortality and morbidity. Alcohol misuse and depression have both been underdiagnosed in men, especially older men, and strategies for screening are explored.

The course closes with suggestions for fostering enhanced healthy behaviors among men, with recommendations for reaching out to men, ensuring appropriate health screening, and encouraging healthy behaviors.

OVERVIEW OF MEN'S HEALTH ISSUES

The concept of men's health emerged in response to the documented trends in greater mortality rates for men compared with women. Over the past decade, attention to the causes of death and disease in men has increased, and a growing body of scientific literature has begun to elucidate gender differences in physiologic, psychologic, and sociologic aspects of disease. These differences have a strong influence on the health of men as well as on the response to treatment and health behaviors.

Men's health lacks the same type of clinical focus as women's health; that is, men's health does not have the equivalent of a specialist (gynecologist) to provide care for the reproductive tract. Care of the male reproductive tract is assumed by primary care physicians, urologists, endocrinologists, reproductive specialists, and possibly, oncologists. The discipline of andrology is in its early stages, and some have proposed that this discipline should be expanded beyond the reproductive tract to include all men's health issues, with a goal of developing appropriate training programs and establishing a distinct specialty [6]. Men's health programs at large academic centers as well as free-standing centers in large cities are providing multidisciplinary diagnostic and management services targeted to men.

As defined by most organizations around the world, the field of men's health encompasses a broad range of health issues, including diseases that are more prevalent among men than women or that differ with regard to risk factors, diagnosis, and treatment. Men's health also addresses the psychologic and social influences on men and acknowledges the need to model healthier attitudes beginning in boyhood.

Several initiatives have helped to promote awareness of men's health among the public, policy arena, and scientific community, including establishment of the Men's Health Network, a nonprofit organization based in Washington, DC, and targeted peer-review journals such as the *Journal of Men's Health* and the *American Journal of Men's Health*.

MORBIDITY AND MORTALITY AMONG MEN

In general, the leading causes of death among men and women are the same; what differs are the age at the time of death, the number of deaths caused by each disease, and the ranking of the causes (***Figure 1***) [7; 8]. The overall death rate in 2019 was higher for male than female individuals (all ages) (846.7 vs. 602.7 per 100,000) [9; 10]. Cardiovascular disease and cancer are the two leading causes of death for both men and women, but a greater percentage of men die of each cause [9; 10]. Deaths related to cardiovascular disease and cancer account for approximately 46% of the total number of deaths among all men [7]. In 2019, the death rate from Alzheimer disease was 30% lower among men than women; the death rates from cerebrovascular diseases, influenza/pneumonia, and chronic lower respiratory diseases were approximately the same for each biologic sex [7; 8]. The causes of death differ within the male population according to age and race/ethnicity, highlighting disparities related to socioeconomic status, cultural differences, access to care, and possibly, genetic predisposition for specific diseases (***Table 1***) [11].

Review of the leading causes of death demonstrates that many men's deaths are potentially avoidable. Most notable is the third leading cause of death for all men: unintentional injuries [11]. Unintentional injuries cause substantially more deaths among men than women, for whom it is the sixth leading cause of death [12]. Suicide is the eighth leading cause of death among all men; this cause of death is not included in the top 10 causes for women. In addition, homicide is among the ten leading causes of death for Black, Hispanic/Latino, and American Indian/Alaska Native men [13; 14; 15]. Several of the other leading causes of death among men are associated with chronic diseases, for which modification of risk factors and early detection can improve outcomes.

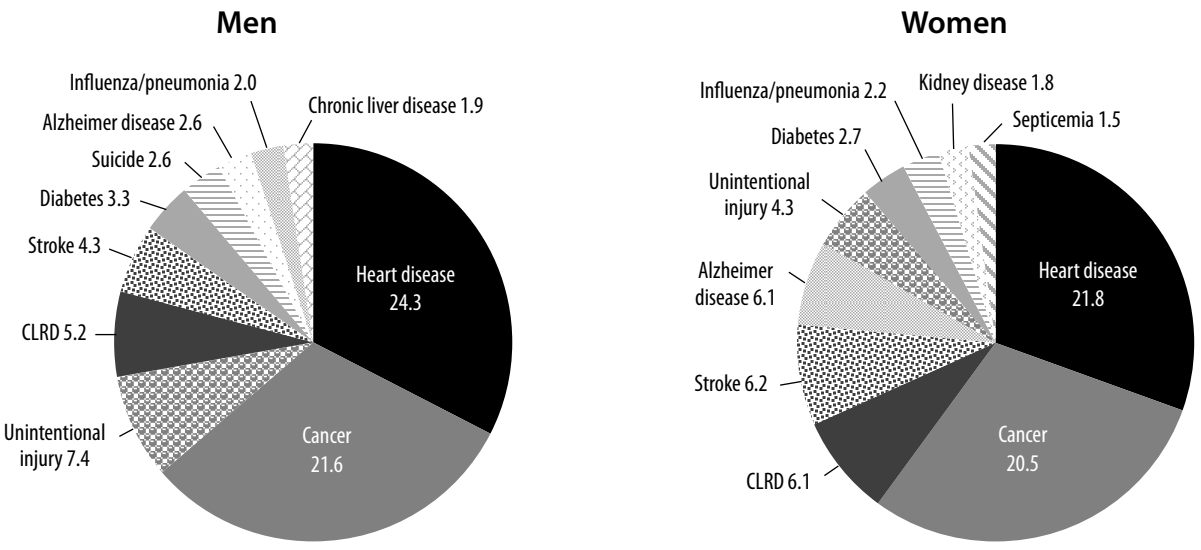
Gender differences exist in the prevalence of specific cancers and in deaths related to cancers [16]. The lifetime probability of being diagnosed with invasive cancer is higher for men than women (***Table 2***) [16]. The rate of deaths associated with cancer of the colon/rectum, urinary bladder, esophagus, and liver and intrahepatic bile duct are higher among men than among women (***Figure 2***) [16]. Although prostate cancer is the most prevalent cancer in men and receives widespread attention, lung cancer is responsible for a greater percentage of cancer-related deaths among men (23% vs. 11%) [16].

MALE GENDER IDENTITY AND IMPLICATIONS FOR HEALTH

An increasing amount of research is supporting a relationship between men's risk for disease and death and male gender identity, and the traditional male role has been shown to conflict with the fostering of healthy behaviors [4; 17]. Male gender identity is related to a tendency to take risks, and the predilection for risky behavior begins in boyhood [17; 18; 19]. In addition, boys are taught that they should be self-reliant and independent and should control their emotions, and societal norms for both boys and men dictate that they maintain a strong image by denying pain and weakness [4; 18; 19].

Issues related to male gender identity have several important implications for health. First, risky behavior is associated with increased morbidity and mortality. Second, the concept of masculinity leads to inadequate help- and information-seeking behavior and a reduced likelihood to engage in behavior to promote health [4; 18; 19]. These behaviors appear to be rooted in a decreased likelihood for men to perceive themselves as being ill or at risk for illness, injury, or death [4]. Third, male gender identity, coupled with lower rates of health literacy, creates special challenges for effectively

THE LEADING CAUSES OF DEATH AMONG MEN AND WOMEN, 2018



CLRD = Chronic lower respiratory disease.

Source: [7; 8] *Figure 1*

TEN LEADING CAUSES OF DEATH FOR MEN ACCORDING TO RACE/ETHNICITY, 2018

Leading Causes of Death	Mortality Rate and Rank					
	All Men	White	Black/ African American	Hispanic/ Latino	Asian/Pacific Islander	American Indian/ Alaskan Native
Cardiovascular diseases	24.4% (1)	24.8% (1)	24.1% (1)	20.2% (1)	23.1% (2)	18.9% (1)
Cancer	22.2% (2)	22.2% (2)	19.7% (2)	19.4% (2)	24.7% (1)	15.9% (2)
Unintentional injuries	6.8% (3)	6.9% (3)	—	11.3% (3)	5.3% (4)	13.7% (3)
Chronic lower respiratory diseases	5.3% (4)	5.8% (4)	3.2% (7)	3.3% (6)	3.2% (6)	3.6% (7)
Stroke	4.2% (5)	4.1% (5)	5.0% (4)	4.7% (4)	6.7% (3)	2.9% (8)
Diabetes mellitus	3.1% (6)	2.9% (6)	4.4% (6)	4.2% (5)	4.2% (5)	5.7% (5)
Suicide	2.5% (7)	2.7% (8)	—	3.1% (8)	2.6% (8)	4.2% (6)
Alzheimer disease	2.5% (8)	2.9% (7)	7.9% (3)	2.3% (9)	2.3% (9)	—
Influenza and pneumonia	2.0% (9)	2.0% (9)	1.7% (10)	3.2% (7)	3.2% (7)	2.2% (10)
Chronic liver disease	1.9% (10)	1.7% (10)	—	4.1% (6)	—	6.1% (4)
Assault (homicide)	—	—	4.5% (5)	2.2% (10)	—	2.3% (9)
Kidney disease	—	—	2.7% (8)	—	2.0% (10)	—
Septicemia	—	—	1.7% (9)	—	—	—

Source: [11] *Table 1*

COMPARISON FOR LIFETIME RISK FOR CANCERS FOR MEN AND WOMEN

Cancer Type	Lifetime Risk	
	Men	Women
All sites	40.2%	38.5%
Lung and bronchus	6.4%	6.0%
Colon and rectum	4.2%	4.0%
Melanoma of the skin	3.7%	2.5%
Non-Hodgkin lymphoma	2.4%	1.9%
Kidney and renal pelvis	2.2%	1.3%
Leukemia	1.9%	1.3%

Source: [16] *Table 2*

TEN LEADING CANCER TYPES FOR THE ESTIMATED NEW CANCER CASES AND DEATHS BY SEX, UNITED STATES, 2022

Estimated New Cases

			Males	Females			
Prostate	268,490	27%			Breast	287,850	31%
Lung & bronchus	117,910	12%			Lung & bronchus	118,830	13%
Colon & rectum	80,690	8%			Colon & rectum	70,340	8%
Urinary bladder	61,700	6%			Uterine corpus	65,950	7%
Melanoma of the skin	57,180	6%			Melanoma of the skin	42,600	5%
Kidney & renal pelvis	50,290	5%			Non-Hodgkin lymphoma	36,350	4%
Non-Hodgkin lymphoma	44,120	4%			Thyroid	31,940	3%
Oral cavity & pharynx	38,700	4%			Pancreas	29,240	3%
Leukemia	35,810	4%			Kidney & renal pelvis	28,710	3%
Pancreas	32,970	3%			Leukemia	24,840	3%
All Sites	**983,160**	**100%**			**All Sites**	**934,870**	**100%**

Estimated Deaths

			Males	Females			
Lung & bronchus	68,820	21%			Lung & bronchus	61,360	21%
Prostate	34,500	11%			Breast	43,250	15%
Colon & rectum	28,400	9%			Colon & rectum	24,180	8%
Pancreas	25,970	8%			Pancreas	23,860	8%
Liver & intrahepatic bile duct	20,420	6%			Ovary	12,810	4%
Leukemia	14,020	4%			Uterine corpus	12,550	4%
Esophagus	13,250	4%			Liver & intrahepatic bile duct	10,100	4%
Urinary bladder	12,120	4%			Leukemia	9,980	3%
Non-Hodgkin lymphoma	11,700	4%			Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	10,710	3%			Brain & other nervous system	7,570	3%
All Sites	**322,090**	**100%**			**All Sites**	**287,270**	**100%**

Source: Reprinted with permission of Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2022. CA Cancer J Clin. 2022;72(1):7-33. *Figure 2*

COMPARISON OF RISKY BEHAVIORS IN YOUTH (9th THROUGH 12th GRADES)		
Behavior	**Male Respondents**	**Female Respondents**
Did not always wear a seat belt	43.3%	42.7%
Rode with a driver who had been drinking alcohol	15.6%	17.5%
Texted or e-mailed while driving	39.6%	38.4%
Drove after drinking alcohol	7.0%	3.6%
Carried a weapon (gun, knife, or club)	19.5%	6.7%
Was in a physical fight in the previous 12 months	28.3%	15.3%
Currently smoke cigarettes daily	6.9%	4.9%
Currently use smokeless tobacco	5.8%	1.6%
Currently use electronic vapor product (e-cigarettes, e-cigars, e-pipes, vape pipes, vaping pens, e-hookahs, hookah pens)	32.0%	33.5%
Had >5 drinks of alcohol within a couple of hours on >1 of the previous 30 days	12.7%	14.6%
Ever used marijuana	37.0%	36.5%
Drove after using marijuana	14.6%	11.3%
Ever misused prescription opioids	12.4%	16.1%
Ever used cocaine	4.9%	2.7%
Ever used heroin	2.3%	1.0%
Ever used methamphetamines	2.7%	2.7%
Source: [23]		*Table 3*

communicating health messages to men [5; 20; 21]. Gender differences in health-related behaviors are consistent across racial/ethnic populations, although specific behaviors vary according to race/ethnicity [17].

Risky Behavior

Risky behavior affects health and well-being beginning at a young age. The overall rate of fatal injuries is approximately two times higher among boys than girls (0 to 19 years of age) [22]. Motor vehicle accidents are the leading cause of death for both genders, especially in the age category of teenage drivers (15 to 19 years of age). Although not all of these injuries and deaths are related to risky behavior, Youth Risk Behavior Surveillance (YRBS) data indicate that many of them are related; other risky behaviors identified in this survey are related to morbidity and mortality in adolescence and are also contributors to habits that affect health in adulthood. The 2019 YRBS showed that the rate of risky behaviors is predominantly higher among male respondents (***Table 3***) [23]. The rates of many of these behaviors continued to be higher among male adults (***Table 4***), which plays a role in premature deaths among men [1; 24].

Men's predilection for risky behavior is reflected in the high rate of unintentional injury, which accounts for 7.4% of deaths among men (compared with 4.3% for women) [7; 8]. There is wide variation in this rate across race/ethnicity, with much higher rates among American Indian/Alaska Native men (13.7%) and Hispanic/Latino men (11.3%) [11]. The trend of more fatal unintentional injuries among men is evident in countries around the world; an analysis of accidental deaths among men and women in 36 countries showed higher rates for men [2]. Across all age-groups, the rates were higher in the United States than the median rate for all countries. Accidental deaths are related primarily to motor vehicle injuries, violence, and occupation, and the rates in all categories are higher for men than for women. The rate of death related to motor vehicle injuries for men is slightly higher than for women (16.0 vs. 6.3 per 100,000), and the percentage of fatal unintentional firearm-related injuries deaths occur overwhelmingly more often among men (82.7%) than women (17.3%) [25]. Similarly, fatal occupational injuries occur predominantly in men (57% vs. 6%) [26].

Substance misuse plays a significant role in both risky behavior and the development of chronic diseases. As demonstrated by the YRBS data, the use of tobacco, alcohol, and illicit drugs begins in the teenage years, with more boys than girls engaging in such behavior [23]. One exception appears to be prescription opioids, which are more likely to be misused by female adolescents than male adolescents. Among adults, substance misuse continues to be more prevalent among men than women [27]. Misuse of tobacco, alcohol, and drugs are associated with high rates of unintentional injuries, violence, STIs, and masking of depression [25; 28; 29; 30].

RISKY BEHAVIOR AMONG ADULTS		
Behaviors[a]	**Men**	**Women**
Non-seat belt use	11.6%	7.2%
"Heavy" drinking (five or more drinks on the same occasion on at least five days of the last month)	8.2%	4.0%
Five drinks or more in a day at least one day within the previous month	28.5%	20.7%
Current smoking	15.6%	12.0%
Use of illicit drugs[a]		
Any illicit drug (past month)	14.0%	9.5%
Cannabis (past month)	12.3%	8.0%
Psychotherapeutic drug (nonmedical use in past month)	2.1%	1.9%
[a]Data for behaviors are based on individuals 18 years of age and older; the data on use of illicit drugs are based on individuals who were 12 years of age and older.		
Source: [1; 24]		*Table 4*

The rate of tobacco use among men has declined over the past decade, but the rate continues to be higher than that among women [31]. The Centers for Disease Control and Prevention (CDC) estimates that men who smoke increase their risk of death from lung cancer by 25 times, with tobacco being the cause of approximately 90% of all lung cancer deaths in men [32]. In addition, smoking is a significant risk factor for many cancers, especially those that are more prevalent among men, and is linked to a two to four times greater likelihood of cardiovascular disease or stroke [32].

Excessive alcohol use is the third leading lifestyle-related cause of death for both men and women, and long-term use of alcohol is a well-recognized contributor to several chronic diseases [33]. Even consumption that is considered to be less than "hazardous" (three to five drinks per day) has been associated with increased morbidity and mortality [34].

Help- and Information-Seeking Behavior

Help- and information-seeking behavior related to male gender identity is another factor that affects men's health. In general, men are reluctant to seek health care or talk about their health because they see such help-seeking as a sign of weakness or vulnerability and a threat to their masculinity [4; 35; 36]. These reports are substantiated by data on utilization of healthcare resources, which indicate that men have fewer office visits to doctors or other health care professional than women; in 2018, 23.9% of men had no office visits, compared with 12.5% of women [37]. In addition, men are more likely to lack a usual source of health care (18.6% vs. 10.7%) [37]. Men have reported several reasons for not having a usual source of care, and the reasons vary among racial/ethnic populations [39]. The reason given most often is that they are seldom or never sick, and this may be related to men's perceptions of invulnerability [39; 40]. Other reasons given include not finding time and not being able to take time away from work [38]. Cultural values, such as *machismo*, lead many Hispanic men to avoid health care until there is no other choice [40]. This may contribute to the low rate of healthcare use among Hispanic men, which is the lowest across racial/ethnic populations [40]. Other reasons for the low use of healthcare services among Hispanic men are lack of health insurance, low understanding of the healthcare system, fear of poor functional outcomes, and a low perception of the quality of the patient-clinician interaction [40]. In the Black population, men have reported to avoid healthcare services because of fears and concerns about their negative health behaviors and history [41].

Lower rates of healthcare use among men have a negative impact on preventive care, and rates of routine health assessments and recommended vaccinations and screening procedures have been lower among men than among women [42]. Several factors contribute to the avoidance of screening tests, including men's belief that they are healthy; their focus on their present, rather than future, health; the need for more information about the screening procedure; and other issues related to masculinity [42]. For example, Black men have reported avoiding screening for prostate and colorectal cancer because they see these procedures as "violating their manhood" [41; 43].

Among men who do have physician office visits, many are not forthcoming about symptoms or information they seek [44]. Because of their traditional discomfort with expressing feelings and emotions, they are less likely to seek help for psychosocial problems or emotional symptoms [17; 45]. Men tend to be more motivated to seek health care for male-oriented conditions, such as erectile dysfunction or sports-related injuries, or when their health or symptoms interfere with their routine activities [45].

Communicating Effectively with Men

Effective communication is essential in the healthcare setting but can be challenged by several factors. Specific challenges in communicating with men are related to male gender identity as well as to low health literacy and language and cultural barriers.

Male Gender Identity

Men's beliefs about masculinity and traditional male roles affect health communication, and healthcare practitioners should consider male-specific beliefs and perceptions when communicating with male patients. For example, because men tend to focus on present rather than future health, concepts of fear, wellness, and longevity often do not work well in health messages [40]. Instead, healthcare practitioners should focus more on "masculine" concepts, such as strength, safety, and performance, all of which tie into men's perceptions of their roles as providers and protectors. To address men's reluctance to admit pain, practitioners should avoid asking questions such as "Do you have pain?" and instead use phrases such as "Most men I see with this condition say they have quite a bit of pain—what about you?" Using numbers/statistics and metaphors relating the body to a machine may also help to communicate effectively by addressing male gender identity. In addition, practitioners should be nonjudgmental about their male patients' health and risk behaviors and develop open lines of communication to encourage them to express their health concerns.

Health Literacy, Language, and Culture

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 [21; 46]. The findings of the assessment demonstrated that the rate of "below basic" literacy was higher among men than women (16% vs. 12%) [21]. Although the rate of "basic" health literacy was similar for men and women, rates of "intermediate" and "proficient" health literacy were lower for men [21]. Similar rates of health literacy have been found in subsequent studies, with rates of adequate health literacy consistently lower among men and even lower among non-White men [47; 48]. In one study, the rate of adequate health literacy was 48% among White men (compared with 63% among White women) and 23% among non-White men (compared with 30% among non-White women) [48].

Recognition of the importance of adequate health literacy to good health outcomes has led to assessment of health literacy being deemed "the newest vital sign," with development of an assessment tool by that name [48; 49]. The Newest Vital Sign (NVS) tool has been shown to demonstrate the health literacy status in fewer than three minutes, with results that are comparable to those of more extensive literacy tests [48]. Clinicians are encouraged to use this tool to assess the literacy of their patients, especially those of racial/ethnic minorities, and to adapt discussions to literacy levels and provide low-literacy educational resources. Compounding health literacy are language and cultural barriers, which have the potential for far-reaching effects, given the growing percentages of racial/ethnic populations. According to U.S. Census Bureau data from 2020, 21.5% of the American population speak a language other than English, and of those, 8.2% speak English less than "very well" [50]. Clinicians should ask their patients what language they prefer for their medical care information, as some individuals prefer their native language even though they have said they can understand and discuss symptoms in English [51]. Translation services should be provided for patients who do not understand the clinician's language. "Ad hoc" interpreters (family members, friends, 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 [52]. 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 [52]. 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 [52]. Individuals with limited English language skills have actually indicated a preference for professional interpreters rather than family members [53].

Most important, perhaps, is the fact that clinical consequences are more likely with ad hoc interpreters than with professional interpreters [54]. 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 [55; 56].

Clinicians should use plain language in their discussions with their patients who have low literacy or limited English proficiency. They should ask them to repeat pertinent information in their own words to confirm understanding, and reinforcement with the use of low-literacy or translated educational materials may be helpful.

MALE-SPECIFIC DISORDERS

Among male-specific disorders, prostatic conditions are perhaps of most concern to men and have raised the most questions in the healthcare community about diagnosis, screening, and treatment. Sexual health issues, such as premature ejaculation and erectile dysfunction, are also of substantial concern to men, and treatments for these conditions gained increased attention beginning in the late 1990s.

The prevalence of many STIs is on the rise, especially among younger men, posing a significant public health problem [57]. Infertility is an issue for many younger men, and interest in late-onset hypogonadism has increased, primarily because of the debate about the use of testosterone replacement therapy. Much attention has also been focused on the unique healthcare needs of a minority population—MSM. (This term has become preferred as a more accurate description because of the variation in how such men identify themselves sexually [58].) Another minority population is that of men with breast cancer, a disease that has become more prevalent since the 1980s. The diseases and conditions noted here by no means represent all of those related to the health care of men. Topics were chosen on the basis of their impact on the overall health of men and the implications for care.

Primary care and family medicine physicians and other general healthcare providers are at the forefront of managing all of these male-specific conditions. Consultation with and referral to specialists, such as urologists, endocrinologists, reproductive specialists, and oncologists, should be carried out as appropriate, and follow-up should be continued with the primary healthcare provider.

DISEASES AND CONDITIONS OF THE PROSTATE

Prostate tissue undergoes changes as men age, and as such, prostatic conditions predominantly occur in older men. The three primary problems related to the prostate are prostatitis, BPH, and prostate cancer. These conditions can be challenging to diagnose because lower urinary tract symptoms, such as frequency, urgency, and dysuria, can be associated with all three conditions. Furthermore, the most serious of the prostate conditions—prostate cancer—usually produces no symptoms in the early stage of the disease. In addition to the diagnostic challenge created by similar, or no, symptoms, the interpretation of prostate-specific antigen (PSA) levels is difficult, and decisions regarding who and when to screen for prostate cancer are not easy.

PROSTATITIS

Inflammation of the prostate is classified into four categories according to a system developed by the National Institutes of Health (NIH) International Prostatitis Collaborative Network [59]. These categories are:

- Acute bacterial prostatitis
- Chronic bacterial prostatitis
- Chronic prostatitis (nonbacterial)/chronic pelvic pain syndrome (subcategorized as A [inflammatory] and B [noninflammatory])
- Asymptomatic inflammatory prostatitis

Both acute and chronic bacterial prostatitis occur in approximately 5% to 10% of men with symptoms related to prostatitis. Chronic nonbacterial prostatitis/chronic pelvic pain syndrome is the most common type, occurring in approximately 90% of symptomatic men [60]. These three types of prostatitis are addressed here; asymptomatic inflammatory prostatitis is an incidental finding during evaluation of another genitourinary condition such as prostate cancer or infertility [61].

It has been estimated that prostatitis accounts for approximately 2 million outpatient visits per year in the United States, with a direct cost of care of nearly $4,000 per patient per year [61]. The condition can have a substantial impact on the quality of life, causing pain and sexual dysfunction, as well as decreased libido and erectile and ejaculatory dysfunction [62; 63].

Chronic prostatitis/chronic pelvic pain syndrome has the greatest impact on the quality of life of all types of prostatitis. Studies have found that the effect of chronic pelvic pain syndrome on the quality of life is similar to that of angina, congestive heart failure, diabetes mellitus, and Crohn disease [61]. Symptoms fluctuate over time; one study showed that 43% of men had symptoms within 11 months of follow-up, and another showed that 31% of men had moderate or marked improvement during two years of follow-up [64; 65]. Chronic prostatitis/chronic pelvic pain syndrome also causes patient anxiety at the initial visit. Most men with symptoms worry that they have an infection (71%) or cancer (68%), and concerns at one-year follow-up have included worsening symptoms without treatment, cancer, infection, and need for surgery [65]. These concerns have led to an increased number of physician visits [65].

Prevalence

The prevalence of prostatitis has been reported to be approximately 8%, ranging from about 2% to 10% [66]. In patients younger than 35 years of age, the most common variant of the syndrome is acute bacterial prostatitis. Among older patients, nonbacterial prostatitis (NIH types II and IV) is the most common [67]. The results of studies have suggested that the symptoms of prostatitis increase the risk for BPH, lower urinary tract symptoms, and prostate cancer [66].

Etiology

The cause of acute and chronic bacterial prostatitis is usually lower urinary tract infection with gram-negative organisms, most notably *Escherichia coli* [60; 61]. Most men with prostatitis, however, have no evidence of urinary tract infection [61]. Other causes may include a primary voiding dysfunction problem; presence of *Chlamydia trachomatis*, *Ureaplasma* species, or *Trichomonas vaginalis*; uncommon organisms (e.g., *Mycobacterium tuberculosis*); HIV; cytomegalovirus; and inflammatory conditions (e.g., sarcoidosis) [67].

The risk factors for prostatitis have not been clearly defined. In a study of 463 men with chronic prostatitis/chronic pelvic pain and 121 asymptomatic age-matched controls, the lifetime prevalence of several self-reported medical conditions were significantly greater among men with prostatitis, specifically neurologic disease (41% vs. 14%); hematopoietic, lymphatic, or infectious disease (41% vs. 20%); psychiatric conditions (29% vs. 11%); nonspecific urethritis (12% vs. 4%); and cardiovascular disease (11% vs. 2%) [68]. The authors of that study noted that more research is needed to determine if such conditions contribute to the pathogenesis of chronic prostatitis/chronic pelvic pain. A history of STIs has been noted to be associated with an increased risk for prostatitis symptoms [66].

Diagnosis

Several other urogenital conditions should be considered in the differential diagnosis of prostatitis, including BPH, cystitis, erectile dysfunction, prostate cancer, STI, and urolithiasis [69; 70; 353]. Of the four types of prostatitis, acute bacterial prostatitis is the easiest to diagnose and treat. Patients with acute prostatitis present with irritative symptoms (dysuria, urinary frequency, and urgency), and obstructive voiding symptoms (hesitancy, incomplete voiding, straining to urinate); the syndrome may also include signs of systemic infection, such as chills and fever [70; 353]. Pain most commonly occurs in the prostate/perineum and scrotum and/or testes; pain referred to the penis or lower back also occurs [70]. Urine samples should be cultured to determine the causative micro-organism.

Chronic bacterial prostatitis is distinguished from acute disease by time, being defined by persistence of symptoms for at least three months, and systemic symptoms are usually absent [58; 70]. The condition should be suspected when the patient's history includes recurrent urinary tract infections, usually with the same bacterial strain [61]. The patient should complete an NIH Chronic Prostatitis Symptom Index to obtain a baseline score for the severity of symptoms [59]. This index includes questions related to three domains—pain, urinary symptoms, and quality-of-life impact—and has been shown to be a valid, reliable tool for measuring prostatitis symptoms [70; 71]. Computed tomography (CT) can determine if there are structural or functional abnormalities of the urinary tract [60; 61].

The diagnostic evaluation for acute or chronic bacterial prostatitis includes a urinalysis and urine culture [61; 70]. When acute prostatitis is suspected, digital rectal exam should be performed gently so as not to precipitate bacteremia and sepsis. The prostate will usually be enlarged, boggy, and tender, though absence of tenderness on initial examination does not exclude the diagnosis of prostatitis. There are no standardized criteria for the diagnosis of chronic prostatitis/chronic pelvic pain syndrome [61; 69]. The Meares-Stamey four-glass test was developed in the late 1960s to screen for prostatitis; the test involves collecting urine samples before and after prostatic massage, as well as collecting prostatic fluid during the massage [72]. Cultures are done on the specimens, and the presence of micro-organisms in the prostatic fluid indicates chronic prostatitis [61; 72]. The accuracy and reliability of the test has not been established, and studies have shown that the test is not used often, even by urologists [61; 69]. There is also a two-glass version of the test that has correlated well with the four-glass version, but that, too, is not often used [61]. The Meares-Stamey test is not helpful for diagnosing chronic pelvic pain syndrome. Men who have substantial lower urinary tract symptoms and pelvic pain may be candidates for urodynamic evaluation, as voiding dysfunction is common in such cases [61].

Treatment Options

No U.S.-based guidelines have been developed, to date, for the treatment of prostatitis, but the European Association of Urology included recommendations for the treatment of prostatitis in its 2008 guidelines on the management of urinary and male genital tract infections [70]. Most patients with bacterial prostatitis can be managed as outpatients with oral antibiotics (e.g., a fluoroquinolone or trimethoprim-sulfamethoxazole) and close follow-up. Hospitalization and broad-spectrum parenteral antibiotics (e.g., piperacillin/tazobactam or ceftriaxone plus ciprofloxacin) should be considered in patients who are systemically ill, are unable to urinate voluntarily, or have risk factors for antimicrobial resistance [70; 353]. An aminoglycoside may be added to any of these antibiotics as initial therapy [70]. A fluoroquinolone is the preferred choice for oral therapy because of the spectrum of antibacterial activity and good penetration into prostatic tissue. Duration of antibiotic treatment should be individualized in relation to duration of symptoms and clinical response; 10 to 14 days will suffice for most acute cases of prostatitis, but 21 to 28 days may be required for those with a more subacute onset or slow resolution of symptoms.

For chronic bacterial prostatitis, the choice of antibiotic depends on the sensitivity of the micro-organism, and the antibiotic should be one that penetrates the prostate [61]. The typical first-line treatment is a four- to six-week course of a fluoroquinolone, and treatment is usually more effective if begun soon after symptoms begin [61; 70; 73; 74]. Trimethoprim-sulfamethoxazole may also be considered [70].

Treatment for chronic prostatitis/chronic pelvic pain syndrome is complex; evidence on the effect of traditional treatment options has been conflicting, and treatment options are often not effective in managing symptoms. The most commonly studied pharmacologic options are antibiotics, alpha-blockers, anti-inflammatory agents, steroid inhibitors, and muscle relaxants, and often, a combination of these agents provides the most effective management [74]. Antibiotics, particularly fluoroquinolones, have improved symptoms, even in some patients in whom a bacterial cause has not

been identified [74]. Studies have shown that an antibiotic and an alpha-blocker is more effective than an antibiotic alone [70]. A meta-analysis showed that alpha-blockers, antibiotics, and a combination of the two all significantly improve symptoms (according to scores on the NIH Chronic Prostatitis Symptom Index), with the combination providing the greatest benefit [75]. However, another meta-analysis showed that these same agents—alone and in combination—were not associated with a statistically or clinically significant decrease in symptom scores [76]. The combination of an alpha-blocker (doxazosin) with an anti-inflammatory agent (ibuprofen) and a muscle relaxant (thiocolchicoside) led to a statistically and clinically significant reduction in the total score on the NIH Chronic Prostatitis Symptom Index in one systematic review; according to the findings of another systematic review, the three-agent combination was not superior to monotherapy [74; 76]. Researchers have cautioned that publication bias may cause overestimation of the beneficial effects of alpha-blockers and that the placebo effect has been significant in many studies [75; 76]. Addressing a hypothesis that the pain related to chronic prostatitis may have a neuropathic origin, pregabalin has been evaluated as a management strategy, but a systematic review found that the drug did not improve symptoms and caused side effects in a large percentage of men [77].

Trigger point release/paradoxical relaxation training to release trigger points in the pelvic floor musculature was found to significantly improve symptoms in men who had chronic prostatitis/chronic pelvic pain syndrome [63]. Seventy percent of the men in the study had a significant decrease in the score on the NIH Chronic Prostatitis Symptom Index, with improvement in pelvic pain, urinary symptoms, libido, ejaculatory pain, and erectile and ejaculatory dysfunction [63].

BENIGN PROSTATIC HYPERPLASIA

Benign prostatic hyperplasia (BPH), also referred to as benign prostatic hypertrophy, is a histologic diagnosis that refers to the proliferation of smooth muscle and epithelial cells within the prostatic transition zone [78]. BPH is one of the most common conditions among aging men. The onset of lower urinary tract symptoms usually begins after 40 years of age, increasing in prevalence and severity with age [78]. Serious complications and mortality are rare, but the condition has an impact on the quality of life, with symptoms that interfere with normal daily activities and sleep [78]. Complete evaluation is necessary for an accurate diagnosis of BPH; the condition must be differentiated from prostate cancer, which is associated with similar early symptoms. In addition, early detection of BPH leads to early treatment, which can control progression of the disease, preventing such complications as urinary tract infection, acute urinary retention, and obstructive nephropathy [79].

Prevalence and Etiology

The prevalence of BPH increases with age, from approximately 8% of men 31 to 40 years of age to approximately 90% of men in their 80s [80; 81]. Risk factors identified in one study included increased age, prostatic volume, and peak urinary flow rate [82]. Other factors, including some that are modifiable, include obesity, diet, dyslipidemia, hypertension, alcohol use, and smoking [83]. The relative risk for BPH (and common comorbidities) may be higher for Black and Hispanic men than for White men and is thought to be related in part to genetic differences based on race/ethnicity; however, observational studies have produced variable results [81; 84].

Diagnosis

As previously noted, distinguishing BPH from other prostate-related diseases is often difficult, as lower urinary tract symptoms are similar for a variety of conditions. The American Urological Association (AUA) evidence-based guidelines for the management of BPH, updated in 2021, recommend the following tests [78]:

- Medical history
- Assessment of lower urinary tract symptoms
- Determination of severity and bother of symptoms
- Physical examination
- Urinalysis

Determination of a serum PSA level is also recommended if the patient has a life expectancy of more than 10 years (and the diagnosis of prostate cancer will alter management), and a frequency-volume chart is recommended if substantial nocturia is a predominant symptom [78]. Routine measurement of a serum creatinine level is not recommended as part of the initial evaluation of men with lower urinary tract symptoms related to BPH [78].

The National Institute for Health and Care Excellence recommends offering men with lower urinary tract symptoms information, advice, and time at initial assessment to decide if they wish to have prostate-specific antigen (PSA) testing if their symptoms are suggestive of benign prostatic enlargement.

(https://www.nice.org.uk/guidance/cg97. Last accessed June 6, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

In obtaining a history, clinicians should ask about urinary tract symptoms, sexual function, previous surgical procedures, and general health issues in an attempt to identify other causes of voiding dysfunction or comorbidities that may complicate treatment. Diabetes, cerebrovascular disease, and Parkinson disease can cause urinary symptoms secondary to neurogenic bladder, and STIs or trauma may cause urethral stricture [85]. It may be appropriate to have the patient keep a diary of voiding habits (frequency, volume, etc.) [78].

Assessment of symptoms is an integral aspect of the initial evaluation for BPH, as it helps to determine the severity of disease. The International Prostate Symptom Score (IPSS) (previously called the AUA Symptom Index) is a validated, self-administered symptom frequency and severity assessment questionnaire originally developed by the AUA Measurement Committee [78]. The IPSS is a widely available, seven-question assessment tool that has been validated for clarity, test/retest reliability, internal consistency, and criteria strength [78; 86]. The IPSS addresses [86]:

- Urinary frequency
- Hesitancy
- Nocturia
- Incomplete emptying
- Urgency
- Weak urinary stream
- Intermittence

Symptoms should be discussed with the patient and questions addressed as necessary [78].

The physical examination should include a digital rectal examination (DRE) to determine the size, consistency, and shape of the prostate [78]. A symmetrically firm and enlarged prostate by DRE is indicative of BPH [79]. The true size of the prostate is often underestimated by DRE compared with transrectal ultrasound [78]. Examination should also include neurologic evaluation to assess the patient's general mental status, ambulatory status, neuromuscular function of the lower extremities, and anal sphincter tone [78].

A urinalysis (dipstick test) to screen for hematuria, proteinuria, pyuria, and other abnormalities can help to rule out such conditions as bladder cancer, carcinoma in situ of the bladder, urinary tract infection, urethral strictures, distal urethral stones, and bladder stones, which are less likely if the results of urinalysis are normal [78].

Optional studies that may be used to confirm the diagnosis or evaluate the presence and severity of BPH include post-voiding residual urine measurement (PVR) and uroflowmetry studies [78]. A PVR is useful in determining a baseline ability of the bladder to empty and detecting severe urinary retention that may not be amenable to medical therapy. Uroflowmetry is a simple, office-based procedure, an adjunct to evaluation of lower urinary tract symptoms and probability of bladder outlet obstruction. Flow rates of <10 mL/second have shown a specificity of 70%, a positive predictive value of 70%, and a sensitivity of 47% for bladder outlet obstruction [78].

Treatment Options

According to the AUA guideline, the benefits, risks, and costs of treatment options should be discussed with patients who have moderate-to-severe symptoms (IPSS score of 8 or more) who are bothered enough by the symptoms to consider therapy [78]. The treatment options for BPH include:

- Watchful waiting
- Medical therapy
  (minimally invasive procedures)
- Surgical interventions

The AUA guideline recommends watchful waiting as the preferred approach for men who have mild symptoms (a score of less than 8 on the AUA Symptom Index) [78]. This approach may also be taken for men with moderate-to-severe symptoms (score of 8 or more) who are not bothered by the symptoms and have no complications [87]. Watchful waiting should include yearly evaluations similar to the initial one [78]. Lifestyle changes and behavioral interventions are considered reasonable first-line treatments for all patients. Symptoms may be reduced by avoiding decongestants and antihistamines, decreasing fluid intake (and avoiding caffeine and alcohol) prior to bedtime, and increasing physical activity and weight loss [78].

AUA guidelines recommend offering monotherapy with an alpha-blocker as initial preferred option for patients with bothersome -to-severe symptoms [78]. Clinicians should consider performing a PVR measurement or uroflowmetry prior to treatment intervention. Five alpha-blockers have FDA-approved indications for BPH (***Table 5***). Clinical studies show that all five of these drugs—alfuzosin, doxazosin, tamsulosin, terazosin, and silodosin—are equally effective in terms of symptom relief and expected range of improvement in symptom index (IPSS) score [78]. The choice of alpha-blocker should be based on the patient's age and comorbidities, and different adverse event profiles (e.g., ejaculatory dysfunction, changes in blood pressure).

The adverse events associated with alpha-blockers are orthostatic hypotension, dizziness, fatigue (asthenia), and ejaculatory problems [78]. These drugs should not be used for men who are taking medication for erectile dysfunction, as the interaction between the two drugs can cause profound hypotension [79]. Alpha-blocker agent use also has been associated with the rare complication of intraoperative floppy iris syndrome; patients anticipating cataract surgery should be informed of the risks and advised to discuss these risks with their ophthalmologist [78].

PHARMACOLOGIC THERAPY FOR BENIGN PROSTATIC HYPERTROPHY	
Agent	**Daily Dose**
Alpha-blockers	
Alfuzosin ER (Uroxatral)	10 mg
Doxazosin (Cardura) and doxazosin ER (Cardura XL)	4–8 mg
Silodosin (Rapaflo)	8 mg
Tamsulosin (Flomax)	0.4–0.8 mg
Terazosin (Hytrin)	1–2 mg
5-alpha reductase inhibitors	
Dutasteride (Avodart)	0.5 mg
Finasteride (Proscar)[a]	5 mg
Combination (alpha-blocker and 5-alpha reductase inhibitor)	
Dutasteride/tamsulosin (Jalyn)	1 capsule (0.5 mg dutasteride and 0.4 mg tamsulosin hydrochloride)
Phosphodiesterase 5 inhibitors	
Tadalafil (Cialis)[a]	5 mg
[a]Combination finasteride/tadalafil (5 mg each) may also be used.	
Source: [89; 90; 91]	*Table 5*

Two 5-alpha reductase inhibitors, finasteride and dutasteride, are also approved for treatment of BPH-related symptoms and are recommended options in the AUA guideline [78]. This is less effective than therapy with alpha-adrenergic antagonists for relieving lower urinary tract symptoms, leading to an average improvement of 3 points on the AUA Symptom Index [78]. The advantage of 5-alpha reductase inhibitors is that they also act to prevent progression of disease and reduce the size of the prostate. As such, the AUA notes that these drugs should be used only for men who have evidence of prostatic enlargement [78]. Men should be made aware of the need for long-term therapy with either of these drugs, and clinicians should also discuss the possible adverse events, which include decreased libido, ejaculatory dysfunction, and erectile dysfunction. These effects usually resolve within one year [78; 79].

In 2011, the FDA issued a safety announcement that the Warnings and Precautions section of the labels of 5-alpha reductase inhibitors was revised to include new safety information about the increased risk of a diagnosis of high-grade prostate cancer [92]. The revision came after FDA review of two prostate cancer prevention trials, in which finasteride and dutasteride reduced the incidence of lower risk forms of prostate cancer but were associated with an increased incidence of high-grade prostate cancer [92].

The AUA guideline also supports the use of combination therapy with an alpha-blocker and a 5-alpha reductase inhibitor for men with lower urinary tract symptoms and evidence of prostate enlargement, as demonstrated on volume measurement, PSA level as a proxy for volume, or on DRE [78]. A fixed-dose combination of dutasteride (0.5 mg) and tamsulosin (0.4 mg) is available, and the results at four years showed that, for men with a baseline prostate volume ≥40 mL and PSA level of ≥1.5 ng/mL, the combination led to greater reductions in the relative risk of clinical progression, acute urinary retention, or BPH-related surgery than either drug alone [93].

The AUA guideline also notes that anticholinergic agents are appropriate and effective options for managing BPH-related symptoms in men who do not have an elevated post-void residual and when symptoms are predominantly irritative [78].

Phosphodiesterase type-5 inhibitors have also been shown to be effective for reducing the symptoms associated with BPH [94]. This class of drugs also offers advantages over other drugs in its rapid onset of action, fewer adverse events, and enhanced sexual function [94]. Potential adverse events include back pain, dyspepsia, headache, and dizziness [95]. In 2011, the first phosphodiesterase type-5 inhibitor—tadalafil—was approved by the FDA for BPH-related symptoms, with indications for symptoms in men who have prostate enlargement, with or without erectile dysfunction [95]. Before prescribing tadalafil, clinicians should ensure that patients are not taking drugs that interact with tadalafil, such as nonselective alpha-blockers, nitrates, and cytochrome P450 inhibitors [95].

Saw palmetto, a commonly used alternative therapy for BPH, is not recommended for BPH-related symptoms, as the most recent data have shown no clinically meaningful effect on symptoms [78].

Minimally invasive therapies such as transurethral needle ablation and transurethral microwave thermotherapy are treatment options for men with bothersome moderate or severe symptoms [78]. However, the AUA guideline notes that, although these therapies improve symptoms, flow rate, and quality of life, the outcomes are not as good as those after transurethral resection of the prostate [78].

Surgical interventions are typically reserved for worsening disease and severe symptoms that do not respond to medical treatment. The AUA guideline recommends surgery for patients with renal insufficiency secondary to BPH, refractory urinary retention secondary to BPH, recurrent urinary tract infections, bladder stones, or gross hematuria due to BPH; or symptoms refractory to other therapies [78]. The most common procedure is transurethral resection of the prostate, which comprises 90% of all prostate surgeries done for BPH and is the benchmark for therapy [78; 96]. Open prostatectomy; transurethral laser ablation or enucleation; laser resection; photoselective vaporization; and transurethral incision, vaporization, and resection are other surgical options, and the selection of intervention is based on the surgeon's experience, the patient's anatomy, and a discussion of the benefits and risk of complications [78].

PROSTATE CANCER

Prostate cancer is the most commonly diagnosed cancer among men, accounting for 19% of all cancer diagnoses in men and the second leading cause of cancer-related deaths, responsible for 9% of cancer-related deaths in men [16]. The lifetime risk of a prostate cancer diagnosis is approximately 15% [16].

Prostate cancer is a complex issue for both men and their healthcare providers for many reasons, including variation in tumor biology, lack of specific symptoms, accuracy of levels of PSA and its several derivatives, questions about optimum treatment, and, most notably, controversy surrounding screening.

Prevalence and Etiology

In 2022, the estimated projected number of new prostate cancer diagnoses was 268,490, with 34,500 prostate cancer-related deaths [16]. The majority of newly diagnosed prostate cancers have localized disease. The highest incidence is found among Black men (172.6 per 100,000), and the lowest is among Asian American and Pacific Islander men (55.0 per 100,000) [16]. The death rate related to prostate cancer is also highest for Black men, with a rate that is more than twice that for men of all other races/ethnicities (37.9 per 100,000 vs. 17.8 [White], 21.0 [American Indian and Alaska Native], 15.6 [Hispanic/Latino], and 8.6 [Asian American and Pacific Islander]) [16]. The mortality rate associated with prostate cancer decreased 4.1% per year between 2009 and 2019, in part, because of improvements in early detection and treatment [16].

The known risk factors for prostate cancer are advanced age, Black race, and a family history of the disease (especially when diagnosed at a younger age) [16; 97]. The risk for prostate cancer may also be increased for men with symptoms of prostatitis [66].

Prevention

Several studies have been undertaken to determine the efficacy of chemoprevention agents and dietary supplements to reduce the risk of prostate cancer. The chemoprevention agents evaluated belong to the class of 5-alpha reductase inhibitors, a class of drugs approved for the treatment of BPH. One drug in this class, finasteride, was evaluated in the first large-scale chemoprevention study, the Prostate Cancer Prevention Trial (PCPT), a seven-year study involving nearly 19,000 men 55 years of age or older. In that study, finasteride significantly reduced the prevalence of prostate cancer (18% vs. 24% for the placebo group) [98]. Dutasteride was shown to decrease the risk of prostate cancer in the REDUCE trial, and extended follow-up indicated a low rate of new prostate cancer diagnoses [99; 100]. The initial results of the PCPT and REDUCE trials led the American Society of Clinical Oncology (ASCO) and the AUA to develop a joint guideline recommending finasteride and dutasteride for the prevention of prostate cancer [90]. However, reanalysis of the results of the trials showed that the risk for high-grade prostate cancer was increased and the reduction in prostate cancer risk was seen primarily for less fatal subtypes of prostate cancer that are often not treated [100; 101]. In 2011, the FDA decided against approving the two drugs for the prevention of prostate cancer, noting that the risk-benefit profile is not favorable for chemoprevention [91; 101; 102]. As stated earlier, the FDA revised the labels of all 5-alpha reductase inhibitors to note the increased risk of higher-grade prostate cancer associated with the drugs [92]. The ASCO/AUA guideline was withdrawn, and experts have called for more research to determine whether 5-alpha reductase inhibitors have a role in the prevention of prostate cancer [101; 102; 103].

Dietary supplements have not been shown to substantially reduce the prevalence of prostate cancer. In the Selenium and Vitamin E Cancer Prevention Trial (SELECT), a randomized study of more than 35,000 men, neither of those two vitamins, alone or in combination, prevented prostate cancer in relatively healthy men [104]. A subsequent phase III trial showed that selenium supplementation had no effect on prostate cancer risk among men with high-grade prostatic intraepithelial neoplasia [105]. There is insufficient evidence for the routine recommendation of other dietary supplements, such as soy, milk thistle, omega fatty acids, lycopene, or green tea, to prevent prostate cancer [106; 107; 359].

RECOMMENDATIONS FOR PROSTATE CANCER SCREENING			
Organization	**Year of Publication**	**Screening Recommendation**	**Notes**
American Cancer Society	2010	—	Discuss the potential benefits, risks, and uncertainties associated with prostate cancer screening with men ≥50 years
American Society of Clinical Oncology	2012	Discourage general screening for men with a life expectancy of ≤10 years, as the harms outweigh the benefits	Discuss the individual appropriateness of screening with men who have a life expectancy >10 years
American Urological Association	2013, reconfirmed 2018	No routine screening in men 40 to 54 years of age at average risk	Decisions should be individualized for men younger than 55 years who are at high risk. Shared decision-making should take place for men 55 to 69 years of age, for whom screening is of greatest benefit.
American College of Physicians	2013	No routine screening with PSA for average-risk men younger than 50, men older than 69, or men with a life expectancy of less than 10 to 15 years	Clinicians should inform men 50 to 69 years of age about limited potential benefits and substantial harms of screening and should individualize decision based on patient's general health, life expectancy, and preferences.
U.S. Preventive Services Task Force	2018	No routine screening for men 70 years of age and older. For men 55 to 69 years of age, the decision should individualized.	Clinicians should discuss the potential benefits and harms of screening.
National Comprehensive Cancer Network	2022	—	Offer baseline PSA testing (with DRE) to average-risk men 45 to 75 years of age, or 40 to 75 years of age for Black/African American men and those with germline mutations that increase risk. If serum PSA values <1 ng/mL, repeat screening every 2 to 4 years. Consider PSA testing only in very healthy patients older than 75 years of age.
Source: [97; 102; 108; 114; 115; 116; 117]			*Table 6*

Screening

There is no question that available screening methods and enhanced awareness has led to an increased number of men in whom prostate cancer is diagnosed at an earlier stage. The primary benefit of screening is a lower stage and grade of cancer at the time of diagnosis, and the high rate of localized disease at the time of diagnosis (92% to 96%) reflects, in part, the increased number of cancers that are detected earlier through screening [102; 108; 109]. Despite this benefit, an effect of screening on mortality has not been clearly demonstrated. After 13 years of follow-up in the National Cancer Institute's Prostate, Lung, Colon, and Ovary (PLCO) trial, there was no benefit of annual screening on mortality [110]. A meta-analysis (five randomized controlled trials) similarly demonstrated no effect of screening on prostate cancer-specific or overall mortality [111]. However, data from the European Randomized Study of Screening for Prostate Cancer demonstrated that screening reduced the risk for prostate cancer death by 7% to 9% per year [112].

In addition to a lack of effect on mortality, screening is associated with high rates of false-positive results, overdiagnosis and subsequent overtreatment, and complications. Among men who had four PSA tests, the cumulative risk for at least one false-positive result was 12.9% [102]. Rates of overdiagnosis have been estimated at 17% to 50%, and 23% to 42% of all screen-detected prostate cancers are overtreated [102; 113]. Furthermore, treatment is associated with complication rates of 20% to 50% [102; 114]. These findings led several expert panels to update their screening recommendations (***Table 6***) [97; 102; 108; 114; 115; 116; 117]. Overall, experts recommend against routine screening for most men and emphasize the need to consider life expectancy and the patient's age and risk factors for the disease. The age to start a discussion about screening varies slightly among the guidelines. The AUA guideline notes that decisions about screening should be individualized for men younger than 55 years who are at high risk for the disease (positive family history or Black race) [114]. The guideline also states that the greatest benefit of screening appears to be for men 55 to 69 years of age and strongly recommends shared decision making for men in this age-group. The ACS guideline notes that screening should be discussed beginning at 50 years of age for men at average risk and before 50 years of age for men at higher risk [108]. The NCCN guideline suggests that clinicians talk to patients about the risks and benefits of a baseline DRE and PSA beginning at 40 years of age [97]. The American College of Physicians (ACP) recommends that clinicians inform their male patients, 50 to 69 years of age, about the limited potential benefits and substantial harms of screening [115].

Researchers continue to investigate ways to make screening more effective. Using a higher PSA threshold for biopsy for older men and less frequent screening for men with low PSA levels are strategies that may reduce the risk of overdiagnosis as well as prostate cancer-related mortality [118].

Informed decision making is integral in selecting approaches to screening, with every guideline emphasizing the need to discuss the potential benefits, harms, and limitations associated with screening with their male patients. The American Cancer Society notes that men should receive information about screening directly from their healthcare provider or be referred to reliable and "culturally appropriate" sources [108]. Decision aids can be especially useful in helping men and their healthcare providers weigh the benefits and risks of screening, and studies of decision aids have led to improved knowledge and have increased men's desire for an active role in decision making [108; 114; 119; 120; 121]. The NCCN guideline offers talking points for discussion, and ASCO provides a decision aid tool (https://www.asco.org/sites/new-www.asco.org/files/content-files/practice-and-guidelines/documents/2012-psa-pco-decision-aid.pdf).

Despite the continued emphasis on informed decision making, the percentage of men who report having had a discussion with their healthcare providers about screening has been suboptimal, with a rate of about 63% to 66% of the general male population [122; 123]. Black men were most likely to have had a discussion, and men without a usual source of care were the least likely [123].

For men who choose to have screening for prostate cancer, the combination of DRE and PSA is the preferred method, providing better predictive value than either method alone [102]. The sensitivity of PSA testing is higher than that of DRE, especially for tumors that are more aggressive [109]. However, the PSA level can vary as a result of several factors.

PSA and Its Derivatives

In an effort to enhance the specificity of PSA testing, variations of the PSA test have been developed, including free PSA, PSA density, PSA velocity, and complexed PSA [97]. Each has its benefits and limitations, and the AUA notes that none increases the benefits-harms ratio of screening [114]. Levels of free PSA have been shown to be significantly lower in men with prostate cancer than in men without the disease [97]. The FDA has approved percent-free PSA for the early detection of prostate cancer in men with PSA levels between 4 ng/mL and 10 ng/mL [97].

PSA density is the result of dividing the PSA level by the volume of the prostate, as measured by transrectal ultrasonography, and a higher result suggests a greater likelihood of prostate cancer [97]. Greater PSA density has correlated with the presence of prostate cancer, as well as with the pathologic stage of the tumor and its aggressiveness and progression after treatment [124]. The use of PSA density has been limited by the lack of precision of total PSA, of measurement of prostate volume, and of the need to carry out transrectal ultrasonography [97]. In addition, PSA density does not offer much benefit compared with other PSA derivatives [97]. PSA velocity is the rate at which a PSA level increases over a period of time, and it has been most helpful for longitudinal monitoring of men younger than 50 years of age who have normal PSA levels and no prostate enlargement [97]. A high PSA velocity alone should not prompt biopsy but instead, aid in decision making [97]. The test is not useful for men with PSA values greater than 10 ng/mL [97]. The ratio of complexed PSA to total PSA provides information comparable to the ratio of free to total PSA, and the use of complexed PSA has been approved as a detection aid (in conjunction with DRE) for men 50 years of age or older; however, the test is not widely used in practice [97].

CLASSIFICATIONS OF RISK OF BIOCHEMICAL RECURRENCE				
Risk Level	**Tumor**	**Gleason Score**	**PSA Level (ng/mL)**	**Other**
Very low	T1c	≤6	<10	Biopsy cores: <3 positive, ≤50% cancer in any core PSA density: <0.15 ng/mL/g
Low	T1–T2a	≤6	<10	—
Intermediate	T2b–T2c	7 (or PSA level as noted)	10–20 ng/mL	—
High	T3a (or other criteria)	8–10 (or other criteria)	>20	—
Very high	T3b–T4 (locally advanced)	Primary Gleason pattern 5 (or other criteria)	—	Biopsy cores: >4 with Gleason score 8–10
NCCN = National Comprehensive Cancer Network, PSA = prostate-specific antigen.				
Source: [126]				*Table 7*

Threshold for Biopsy

Prostate cancer is found in about 25% of biopsy specimens, illustrating a problem regarding a well-defined threshold at which to obtain a biopsy specimen [125]. Although most cancer is detected with use of a PSA threshold of 4 ng/mL, some studies have shown that prostate cancer is subsequently found in men with levels in the range of 2.5–4.0 ng/mL [97]. The NCCN concluded that while these values have been used by many, a level of 3.0 ng/mL is supported by trials and would more robustly limit the risk of overdetection. However, there was not a consensus among NCCN panel members regarding limiting the option to biopsy to prespecified PSA thresholds [126]. The NCCN panel also concluded that DRE alone is not an absolute indication for biopsy in men with low PSA, as the positive predictive value of DRE in this population is poor. However, a very suspicious DRE, independent of PSA, could indicate high-grade cancer in men with normal PSA values, and therefore, biopsy should be considered in these men [126].

Diagnosis and Staging

Men with early prostate cancer are usually asymptomatic. More advanced disease may be associated with changes in urinary habits, such as a slowing of the urinary stream, sense of incomplete voiding, nocturia, and frequency, as well as dysuria, hematuria, or pain in the lower back or pelvis. Because many of these symptoms are similar to those linked to benign prostate conditions, prostate cancer cannot be diagnosed on symptoms alone. The diagnostic methods are the same as those used for screening: PSA, DRE, and transrectal ultrasonography. In performing the DRE, the clinician should focus on the size, consistency, and abnormalities within or beyond the gland. Prostate cancers are characteristically hard, nodular, and irregular.

In its 2013 Best Practice Statement on PSA, the AUA emphasizes the importance of PSA in staging, noting that the PSA level predicts response of prostate cancer to local therapy [127]. Response is most likely in men with a PSA level <10 ng/mL [127].

Biopsy of the prostate with analysis of the tissue provides the most definitive diagnostic procedure. It also gives evidence of the aggressiveness of the tumor when cancer is detected. The pathologist quantifies the aggressiveness of the tumor with use of the Gleason score, assigning a number between 2 and 10 (with 10 representing the most aggressive). Pathologic review involves both staging according to the American Joint Committee on Cancer staging manual and classification of the tumor with the Gleason score [128]. Further staging with imaging (CT, MRI, bone scan) is done only for tumors that are confined to the prostate with a Gleason score of 8 or higher or a PSA level of greater than 20 ng/mL or for tumors that extend beyond the prostate or are symptomatic [97]. As part of the Choosing Wisely campaign, the AUA notes that a routine bone scan is not necessary for men with newly diagnosed prostate cancer with a PSA level <20.0 ng/mL and a Gleason score of ≤6 [127].

Treatment Options

Recognizing that many prostate cancers have an indolent natural history, guidelines recommend utilization of a risk stratification classification for patients with newly diagnosed localized disease [358]. Stratification facilitates patient counseling and should be used with a shared decision-making approach in which treatment decisions are based on the patient's estimated life expectancy and the risk of biochemical recurrence [126]. Risk of biochemical recurrence has been classified by the NCCN into five categories (***Table 7***) [126].

ADVANTAGES AND DISADVANTAGES OF ACTIVE SURVEILLANCE FOR PROSTATE CANCER	
Advantages	**Disadvantages**
Ensure that small indolent cancers are not treated unnecessarily	Lack of definitive prompt for treatment may lead to missed opportunity for cure
Avoid side effects of treatment that may be unnecessary	Cancer may progress or metastasize before treatment
Maintain quality of life and normal activities	Treatment of larger, more aggressive cancer may be more complex, with increased side effects
Decrease initial costs	Living with an untreated cancer increases anxiety Must carry out frequent medical examinations and biopsies Timing and value of long-term natural history of untreated disease is undetermined Long-term natural history of untreated disease is uncertain
Source: [126]	*Table 8*

A new prostate cancer grading system was developed during a 2014 consensus conference of the International Society of Urological Pathology (ISUP). The new system resulted in changes to the assignment of Gleason pattern based on pathology. This system assigns grade groups from 1 to 5, derived from the Gleason score. Many experts believe that the ISUP grade groups enable patients to better understand their true risk level and limit overtreatment. The NCCN has accepted the new grade group system. Patients remain divided into very-low-, low-, intermediate-, high-, and very-high-risk groups [126].

The primary options for localized prostate cancer are watchful waiting (also known as active surveillance), radiation therapy (either three-dimensional external-beam radiation or brachytherapy), and radical prostatectomy. Other options include androgen-deprivation therapy (ADT, also referred to as hormone therapy), chemotherapy, cryosurgery, and immunotherapy.

Each treatment option is associated with benefits and harms, and clinicians should discuss each option in detail and provide educational resources and decision aids [129; 130; 131]. To gain a true understanding of a patient's preferences, treatment options should be discussed only after the patient has described his preferences [132]. Clinicians should carefully assess their patients' understanding of treatment options; studies of underserved men have shown low comprehension of common terms used in prostate cancer treatment discussions [133; 134]. Attention should also be paid to how to best communicate risk. A study has shown that such terms as "number needed to treat," "odds ratio," and "relative risk reduction" were confusing to men [135]. In that study, men best understood information when it was presented as an absolute risk reduction and in a positive context; men preferred that treatment options be discussed in terms of the probability of an increase in survival (rather than a decrease in mortality) and that the discussion include the impact of treatment on patient-centered quality-of-life outcomes [135].

Active Surveillance

Active surveillance has also been referred to as watchful waiting, but the terms have not always been defined the same way, and researchers are calling for a distinction between the two terms. Active surveillance denotes an approach in which men with localized, low-risk prostate cancer are followed up closely for clinical signs that prompt definitive treatment with curative intent should this become necessary [136; 358]. Watchful waiting refers to the strategy recommended for asymptomatic patients with prostate cancer and limited life expectancy [358]. Some studies draw further distinction, defining watchful waiting as observation and provision of palliative care when prostate cancer becomes symptomatic, and active surveillance as close follow-up (with DRE, PSA levels, and biopsies) and provision of treatment at signs of disease progression [138]. Patients with a life expectancy of less than five years do not benefit from prostate cancer screening, diagnosis, or treatment as prostate cancer treatment does not improve survival within five years of follow-up [358].

For patients with favorable intermediate-risk prostate cancer, clinicians should discuss with patients the options of active surveillance, radiation therapy, or radical prostatectomy [358]. Choosing active surveillance rather than definitive treatment is difficult because of the myriad advantages and disadvantages to the approach (***Table 8***) [126]. Data on active surveillance have also conflicted. In a cohort of 450 men followed up for a median of nearly seven years, the rate of prostate cancer-specific mortality was low [139]. Two later systematic reviews indicated that the evidence was insufficient to determine whether active surveillance with curative intent was an appropriate option for men with localized prostate cancer [136; 137]. Most recently, radical prostatectomy was compared with active surveillance, and the intervention did not significantly reduce all-cause or prostate cancer-specific mortality through at least 12 years of follow-up [140]. In addition, a cost-effectiveness analysis demonstrated that active surveillance was most effective

and least expensive compared with several interventions (brachytherapy, intensity-modulated radiation therapy, or radical prostatectomy) [138].

The NCCN Panel recommends active surveillance for all men with very-low-risk prostate cancer and a life expectancy of less than 20 years and believes that surveillance should be considered for men with very-low-risk prostate cancer and a life expectancy of 20 years or more [126]. In addition, the Panel recommends active surveillance for all men with low- and favorable intermediate-risk prostate cancer and a life expectancy of less than 20 years and believes that it should be considered for men with low- and favorable intermediate-risk and a life expectancy of 10 years or more [126]. With active surveillance, recommended monitoring is measurement of a PSA level no more than every 6 months, unless clinically indicated, and physical exam with DRE every 12 months [126]. An increase in PSA should prompt re-testing as transient PSA elevations are common; serial PSA increases, new DRE abnormalities, or other concerns for clinical progression should prompt re-evaluation with prostate MRI and possible prostate biopsy [126; 358].

Radiation Therapy

Radiation therapy is an option for men at various levels of risk for biochemical recurrence, except for men for whom active surveillance is recommended [126]. Radiation to pelvic lymph nodes may be considered for men with intermediate risk and should be done for men at high risk [126]. Radiation therapy offers progression-free survival similar to that of prostatectomy while avoiding the complications associated with surgery [126].

The advent of three-dimensional (3D) CRT, which integrates external-beam radiation with CT images, has allowed for the delivery of higher radiation doses but with a lower risk of side effects because of enhanced precision [126]. About half of men will have temporary bladder or bowel symptoms during treatment with external-beam radiation therapy [126]. The disadvantage to external-beam radiation therapy is the time needed for treatment, as the recommended duration of treatment is eight to nine weeks [126].

Intensity-modulated radiation therapy (IMRT), a second-generation 3D technique, has been used increasingly in clinical practice [141]. IMRT reduced the risk of gastrointestinal toxicities and rates of salvage therapy compared with 3D-CRT in some retrospective, population-based studies, but treatment cost was increased [142; 143]. More recently, moderately hypofractionated image-guided IMRT regimens have been tested in randomized trials, but additional research is needed [126].

Brachytherapy has been used increasingly for men with early localized prostate cancer; however, increasing evidence suggests that technical advancements in brachytherapy may have a role in treatment of high-risk localized and locally advanced prostate cancer [126; 144; 145]. This approach is a recommended option as monotherapy for men at low risk and a life expectancy of at least 10 years and in combination with external-beam radiation therapy for men at intermediate risk, regardless of life expectancy [126; 146]. Complications are increased when the two forms of radiation therapy are used together [126]. Brachytherapy alone yields control rates comparable to those of surgery (approximately 90%), and added advantages are short treatment duration, minimal risk of incontinence, and short-term preservation of erectile function; the seeds are implanted in one procedure, and men typically recover in one day [126]. Disadvantages include the need for general anesthesia and a risk of acute urinary retention [126].

Radical Prostatectomy

Radical prostatectomy is an option for men with a life expectancy of at least 10 years who have clinically localized disease that can be completely excised [126]. It also may be an option for men with high-risk disease and for select patients with very-high-risk disease, although several factors (e.g., PSA >10 ng/mL, stage T2b or higher, Gleason score 9 or 10, higher number of biopsy cores with high-grade cancer, more than 50% core involvement) predict unfavorable outcome in these patients [147]. Radical prostatectomy is a salvage option for patients experiencing biochemical recurrence after primary external beam radiation therapy, but morbidity remains significantly higher than when the treatment is used as initial therapy [148; 149]. This treatment option has been most often associated with the highest survival rates but also with side effects that have been reported to have a significant impact on quality of life, such as impotence, incontinence, urethral stricture, and surgery-related morbidity [126; 150; 151]. Despite the potential side effects, the sense of being cancer free has led men who chose to have radical prostatectomy to be satisfied with their decision [152]. Laparoscopic and robot-assisted procedures have been found to yield results similar to those for open procedures, but rates of incontinence and erectile dysfunction may be higher [126]. The AUA notes that no conclusive benefit to pelvic lymph node dissection has been found [127]. Such dissection for clinically localized disease may not be necessary if the PSA is less than 10 ng/nL and the Gleason score ≤6 [127].

Androgen Deprivation Therapy (ADT)

ADT involves medical or surgical castration (with luteinizing hormone-releasing hormone [LHRH] agonists or orchiectomy, respectively). It is recommended as an adjunct to radiation therapy or prostatectomy for men with local or locally advanced disease and at high or intermediate risk for recurrence [126]. Meta-analyses have shown clinical benefit for adjuvant ADT after either radiation therapy or prostatectomy or neoadjuvant therapy before radiation therapy [153; 154].

Both NCCN and ASCO recommend ADT as initial treatment for metastatic prostate cancer [126; 155]. Researchers have evaluated the timing of ADT—early (before symptoms occur) or delayed—and early therapy has provided no overall survival benefit and only a modest decrease in risk for prostate cancer-specific mortality; because of this, the ASCO guideline does not make a recommendation for early ADT [155]. Several studies have demonstrated that intermittent ADT is as effective as continuous ADT for metastatic or locally advanced disease, with better quality of life and fewer side effects [156; 157; 158].

Use of ADT as a primary therapy for men with localized prostate cancer has increased significantly among men at low and intermediate risk, but this approach should not be considered standard [126; 146]. ADT is associated with several adverse events, including osteoporosis, increased risk for fracture, obesity, insulin resistance, and increased risk for cardiovascular disease and diabetes [126].

Chemotherapy

The use of chemotherapy is typically reserved for men with metastatic castration-resistant prostate cancer, and docetaxel-based regimens have been shown to confer survival benefit [159; 160]. The duration of therapy is not well-defined, but 10 cycles were used in the phase III trials in which these regimens were evaluated.

Cryosurgery

Cryosurgery is a minimally invasive procedure that is an option for prostate cancer (of any grade) that is clinically confined to the prostate in men at low, intermediate, or high risk [161]. The five-year biochemical disease-free survival rates have ranged from 48% to 92%, depending on the risk of recurrence, but long-term data on prostate cancer-specific survival are not yet available and there are no clearly defined guidelines for patient selection for cryosurgery as a salvage procedure [161]. The authors of a meta-analysis published in 2007 and updated in 2018 concluded that it was difficult to determine the relative benefits of this treatment because of the poor quality of the available studies [162].

Options for Metastatic Castration-Resistant Prostate Cancer

Since 2010, three agents, an immunotherapy, and a radiopharmaceutical have been approved for metastatic castration-resistant prostate cancer. Cabazitaxel (Jevtana), enzalutamide (Xtandi), and abiraterone acetate (Zytiga) are indicated for treatment following docetaxel [126]. Sipuleucel-T (Provenge), an autologous cellular immunotherapy, is approved for men with metastatic castration-resistant prostate cancer who are asymptomatic or minimally symptomatic. Lastly, radium 223 dichloride (Xofigo) was approved in May 2013 for the treatment of metastatic castration-resistant prostate cancer with bone metastases (but not visceral involvement) [126].

Prognosis

Survival after treatment of prostate cancer is related to the extent of the tumor at the time of diagnosis, and the relative five-year survival rate is 100% for localized or regional prostate cancer [16]. The five-year survival rate is substantially lower (30%) when prostate cancer is metastatic at the time of diagnosis [16].

Follow-up

Primary care physicians, nurses, and other healthcare professionals who see patients on a regular basis play an important role in the follow-up evaluation for men who opt for active surveillance, as well as for those who have been treated by an oncologist. After treatment for prostate cancer, men should be followed up with an annual DRE and PSA testing every 6 to 12 months for five years and annually thereafter [163]. Primary care clinicians can also aid in the management of the side effects of treatment and screening for secondary cancers.

Case Study

Patient A is an active man, 59 years of age, who missed his yearly DRE and PSA. The results of these tests had been within normal limits in all previous examinations. At his next examination, a firm prostate nodule, approximately 2 mm in diameter, is palpated, and the PSA level is 14 ng/mL. A needle biopsy of the prostate is performed within one week of the PSA measurement. The biopsy shows several sites containing cells indicative of adenocarcinoma of the prostate, with a Gleason score of between 8 and 9.

After carefully evaluating the treatment options for an aggressive tumor, Patient A chooses radical prostatectomy and seeks care at an institution where nerve-sparing surgery is performed with the assistance of a robotic, computer-controlled device, to help reduce the risk of adverse events. According to the pathologic evaluation, the tumor is an adenocarcinoma that has extended beyond the capsule of the gland but has not involved the seminal vesicles.

Staging studies, including an MRI of the pelvis and abdomen and a bone scan, confirm the extent of the tumor and demonstrate lack of lymph node involvement or distant metastasis (T3a, N0, M0). Because of the T3a finding, a course of external-beam radiation therapy to the local site is prescribed.

At the three-month follow-up visit, the PSA level has increased to 20 ng/mL, and a bone scan demonstrates multiple skeletal lesions, primarily in the ribs, pelvis, and skull, none of which had been seen on the previous scan. Due to the rapid progression of disease and the metastatic lesions, the patient's survival is estimated to be less than three years.

DISTINGUISHING BETWEEN TESTICULAR TORSION AND EPIDIDYMITIS		
Sign/Symptom	**Testicular Torsion**	**Epididymitis**
Onset of pain	Sudden (<12 hours)	Insidious
Cremasteric reflex	Absent	Present
Tenderness	Diffuse; spermatic cord	Epididymal area
Appearance of scrotum	Usually normal	Edematous, "orange peel" appearance
Testicular lie	High	Normal

Source: [164; 165; 167; 168] *Table 9*

After a discussion with his surgeon, oncologist, and urologist, the patient decides to forego ADT, choosing instead to enroll in a clinical trial for treatment consisting of chemotherapy with docetaxel in combination with the angiogenesis inhibitor bevacizumab over a course of several months. The treatment causes some nausea, malaise, and hair loss, but the patient tolerates the effects well. The primary bothersome adverse effect is oral ulcers, which require topical treatment. The PSA level drops steadily during follow-up, reaching a level of 0.4 ng/mL after approximately six months of treatment.

Patient A continues to feel well after two years of follow-up, and the PSA level has remained at 0.2 ng/mL or less. Incontinence that was present after the surgery has ended, but erectile dysfunction remains, despite the use of medications.

DISEASES AND CONDITIONS OF THE TESTES

Testicular conditions are fairly uncommon but are more prevalent among younger men than older men [164; 165]. As with conditions of the prostate, testicular conditions may be associated with similar symptoms, creating a challenge for accurate diagnosis. When evaluating a man who has acute scrotal pain, a primary objective is to distinguish benign conditions from those requiring immediate intervention and from testicular cancer.

TESTICULAR TORSION

Testicular torsion occurs in approximately one in 4,000 male individuals younger than 25 years of age each year [164]. In 90% of cases, intravaginal torsion is caused by a congenital malformation of the processus vaginalis [164]. Predisposing factors include increased testicular volume, testicles with horizontal lie, history of cryptorchidism, and a spermatic cord with a long intrascrotal portion [166]. Surgery to repair the torsion is necessary to save the testicle; thus, early diagnosis is critical [164; 165].

The most common misdiagnosis of testicular torsion is epididymitis [164; 167]. The first step should be to determine the onset of pain, as testicular torsion is associated with pain of sudden onset; in contrast, the onset of pain is insidious in epididymitis and other conditions [164; 165]. The physical examination also plays an important role in distinguishing testicular torsion from epididymitis. A key distinction is the absence of the cremasteric reflex in testicular torsion, which has been found to have a sensitivity of at least 99% in two studies of boys [167; 168]. To elicit this reflex, the medial thigh is stroked or pinched, which causes contraction of the cremaster muscle and elevation of the testis. If the testicle moves at least 0.5 cm, the reflex is positive [164]. Other distinguishing features include the area of tenderness, appearance of the scrotum, and testicular lie (***Table 9***) [164; 165; 167; 168].

If the diagnosis of testicular torsion is still in question after physical examination or if the onset of pain was 6 to 12 hours previously, color Doppler ultrasonography should be carried out [164; 165]. This imaging study has been found to have a sensitivity of 88% and a specificity of 90% in detecting testicular torsion in boys [169]. Decreased or absent blood flow and rotation of the spermatic cord on the affected side are indicators of testicular torsion [164; 166]. Scintigraphy with technetium 99m pertechnetate has a higher sensitivity, but this modality is not as readily available as ultrasonography in some institutions [164; 170].

A diagnosis of testicular torsion, whether highly suspected or definitive, requires immediate surgical intervention, and a surgical consultation should be obtained [164; 165]. The success rate for manual detorsion has been low (approximately 26%), so this procedure should be avoided as an alternative to surgical treatment [164; 171].

EPIDIDYMITIS

Inflammation of the epididymis affects a small proportion of men. Few epidemiologic studies are available, but the prevalence has been estimated to be approximately 0.29% to 0.9% and is the same across racial/ethnic populations [172]. Acute epididymitis is usually caused by bacterial infection, and the source of the infection varies. For men who are

younger than 35 years of age and sexually active, the source is most commonly an STI. The most frequently identified micro-organisms are *C. trachomatis* and *Neisseria gonorrhoeae* [57; 173]. The diagnosis and treatment of epididymitis caused by STIs are discussed later in this course.

Among men who are older than 40 years of age, epididymitis is usually associated with bacterial infection of the urinary tract. Epididymitis has also been reported as a side effect of the drug amiodarone, used for ventricular arrhythmias [174]. A review of the literature indicated that the time to onset of the condition ranged from 4 to 71 months and developed at a daily dose of 200–800 mg [174; 175]. In many cases, there is no known etiology [176]. When pain, swelling, and/or inflammation persist for more than three months, the condition is considered to be chronic.

Men with acute epididymitis usually present with unilateral pain and tenderness in the testicle [173]. Additional symptoms include dysuria, urinary frequency or urgency, and symptoms related to the source of infection (e.g., fever, chills, or pain). Urinalysis and urine culture should be done to determine the presence of infection [175; 176].

Obtaining a careful history is an important first step in the diagnosis of epididymitis. The practitioner should ask about the sexual history; surgical history, especially in the scrotal area; the location, severity, and frequency of pain; and the presence and duration of symptoms [176]. When symptoms have been present for three months or longer, the Chronic Epididymitis Symptom Index can help determine the impact of symptoms on the quality of life [176].

As stated previously, several findings on physical examination can distinguish epididymitis from testicular torsion [164; 165; 167; 168]. The physical examination should also include evaluation of the abdomen, especially to check for tenderness in the flank and bladder distention, and the inguinal regions [165]. Examination of the scrotum should be carried out bilaterally, assessing the degree of swelling, presence of erythema, and differences in size [165].

Acute infectious epididymitis is treated by addressing the underlying infection, and antibiotics should be chosen according to the causal micro-organism. Symptomatic relief for both infectious and noninfectious epididymitis can be achieved with bed rest, scrotal support and elevation, ice packs, and anti-inflammatory agents or analgesics. If tenderness or swelling persists after treatment with antibiotics or if a mass becomes palpable, further evaluation should be carried out to rule out testicular cancer [173; 177]. Watchful waiting is suggested for chronic epididymitis [176].

Consultation with a urologist may be appropriate for men with complications or with chronic epididymitis [173]. Scrotal exploration may be necessary if abscess, testicular infarction, or pyocele develops. Epididymectomy has been used to treat chronic epididymitis, but the outcomes have varied widely [176].

VARICOCELE

A varicocele is a dilated, tortuous inflammation of the veins of the spermatic cord above the testicle. A prevailing thought has been that the superior mesenteric artery compresses the left renal vein over the aorta, also known as the "nutcracker effect" [178]. This theory has been confirmed by studies that have shown that varicoceles are less common in obese men [178; 179]. It has also been suggested that the condition is caused by damage to the contractile mechanism of the smooth muscle organization of spermatic veins [180]. As a result of anatomic differences, the condition is more common in the left testicle, but advances in imaging have led to reports of high rates of bilaterality [181]. Varicocele can cause discomfort in the scrotal area, but usually the condition is asymptomatic [165].

The frequency of varicocele among adolescents and young adults is approximately 15% to 20%, and the rate is higher among men who have some level of infertility, with reports of 77% and 81% in some studies [181; 182]. A study of older men (mean age: 60.7 years) demonstrated a prevalence of 42% [183].

Varicoceles vary in size, and large ones can be identified through physical examination alone. Varicoceles can have an adverse effect on spermatogenesis, and infertility has been associated with varicoceles that can be palpated [182]. The most significant finding is a feeling of a "bag of worms" when the scrotum is palpated [165; 182]. The varicocele may disappear or be substantially reduced when the patient is recumbent [182]. Smaller varicoceles can be detected by asking the patient to perform the Valsalva maneuver in the standing position [182]. In older men (at least 60 years of age), varicoceles have been associated with significantly smaller and soft testes [183]. Color Doppler ultrasonography is the diagnostic procedure of choice when the findings of the clinical examination are inconclusive [182].

The American Urology Association and the American Society for Reproductive Medicine recommend surgical varicocelectomy be considered in men attempting to conceive who have palpable varicocele(s), infertility, and abnormal semen parameters, except for azoospermic men.

(https://www.auanet.org/guidelines/guidelines/male-infertility. Last accessed June 6, 2022.)

Strength of Recommendation/Level of Evidence: Moderate/B (Applies to most patients in most circumstances but better evidence could change confidence)

The treatment of varicocele depends on several factors, including the age of the patient, the size of the varicocele, the results of semen analyses, and the patient's desire for fertility [182]. Varicoceles in adolescents and young adults have been associated with significant loss of testicular volume and growth arrest of the testes, the risk of which increases with the size of the varicocele [184; 185]. These individuals should be monitored with physical examination and semen analyses to detect changes in testicular function, as earlier treatment will increase the likelihood of recovering normal spermatogenetic function [182; 186]. Advances in minimally invasive procedures and surgeries have led to significant strides in the management of symptomatic varicoceles [187]. Many experts agree that indications for surgical intervention in adolescents are pain, large varicoceles, hypotrophy of the involved testicle, bilateral varicocele, intratesticular varicocele, and abnormal semen parameters on serial evaluation. The ideal method for treating adolescent varicocele has not been clearly established, but the main task is to decrease the number of recurrences and complications while retaining optimum testicular function. Because of this, many surgeons respect the attitude "catch-up growth" [188]. Treatment approaches and outcomes of therapy are discussed more fully in the section on infertility.

TESTICULAR CANCER

Testicular cancers are primarily germ cell tumors and are classified as seminomas and nonseminomas, the latter type being more clinically aggressive [177]. Testicular cancer is rare, accounting for 0.5% of all malignant tumors [177; 190]. However, the worldwide incidence of this type of cancer has been increasing in the past six decades [177]. As with other testicular conditions, this cancer is most common among male individuals 20 to 34 years of age [177; 189]. Early detection results in a cure rate of approximately 95% [177].

Prevalence

In 2019, there were an estimated 283,792 men living with testicular cancer in the United States [190]. In 2022, there will be an estimated 9,910 new cases of testicular cancer and 460 deaths. According to 2000–2019 SEER data, the incidence is highest among non-Hispanic White men (7.3 per 100,000), followed by American Indian/Alaska Native (10.6 per 100,000) and Hispanic men (5.9 per 100,000), Asian/Pacific Islander men (2.4 per 100,000), and Black men (1.5 per 100,000) [191].

Etiology

Among the several risk factors for testicular cancer, the primary one is cryptorchidism, which can increase the risk 11-fold [177]. Other risk factors include a family history of the disease, testicular dysgenesis, and Klinefelter syndrome [177]. A history of cancer in one testicle confers an increased risk (2% to 5%) of cancer in the contralateral testicle over the 25 years following diagnosis [192].

Screening

The USPSTF does not recommend routine screening for testicular cancer—by either clinician examination or self-examination—for asymptomatic adolescent and adult male individuals, as there is no evidence that screening reduces mortality [193]. The USPSTF notes that instead of screening, men should be advised to report testicular problems promptly, as cure rates are high for any stage of testicular cancer [193].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The European Association of Urology recommends high-frequency (i.e., >10 MHz) testicular ultrasound be used to confirm a testicular tumor even in the presence of a clinically evident testicular lesion.

(https://uroweb.org/guidelines/testicular-cancer. Last accessed June 6, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

Diagnosis

Testicular cancer usually presents as discomfort or swelling in the testicles that is suggestive of epididymitis or orchitis [177]. Physical examination will demonstrate a palpable mass [177]. Occasionally, the patient may note tender or swollen breasts or loss of sex drive.

According to the NCCN guideline for the treatment of testicular cancer, testicular ultrasonography is optional if a diagnosis is obvious from the physical examination, but the guideline notes that this diagnostic test is usually done to define the lesion [177]. Both the NCCN and ASCO recommend measuring serum levels of alpha-fetoprotein (AFP), human chorionic gonadotropin (beta-hCG), and lactate dehydrogenase (LDH) to help determine if the testicular mass is a germ cell tumor and, if so, whether it is a seminoma or a nonseminoma [177; 194]. A nonseminoma is associated with an elevated AFP level; in contrast, an elevated level of beta-hCG, with a normal AFP level, usually indicates a seminoma [177]. Additional evaluation should include a chest x-ray and CT of the abdomen and pelvis to determine if lymph nodes are involved [177]. If metastatic disease is suspected, further imaging studies, such as bone scan, magnetic resonance imaging, or positron emission tomography, may be necessary. Open biopsy is not usually performed [177].

Treatment Options

Men with suspected testicular cancer should be referred to an oncologist who will discuss treatment options, which include orchiectomy and radiation therapy or chemotherapy, depending on the type of tumor and the stage of disease. Lymph node dissection may also be necessary for metastatic disease. The possibility of sperm banking should be discussed before any type of treatment is initiated [177].

Treatment options for early-stage seminoma (stage I, confined to the testicle and epididymis) are active surveillance (preferred), single-agent carboplatin (one or two cycles), or radiation therapy [177].

Radiation therapy is recommended for stage II seminoma (involvement of nearby lymph nodes), with the treated area extended to include the ipsilateral iliac lymph nodes [177]. If radiation is contraindicated, chemotherapy with three cycles of bleomycin, etoposide, and cisplatin (BEP) or four cycles of etoposide and cisplatin (EP) is recommended. If chemotherapy is given, both regimens are recommended [177]. Chemotherapy with EP or BEP is recommended for stage III seminoma (involvement of distant lymph nodes and/or viscera) [177].

Treatment options for nonseminoma include surveillance, chemotherapy, and retroperitoneal lymph node dissection [177]. Selecting the appropriate therapy involves consideration of many factors, including the extent of disease in the lymph nodes, the levels of serum tumor markers before and during treatment, radiographic findings, and the commitment of the patient to adhere to surveillance protocols that involve frequent blood work and CT [177]. Chemotherapy involves either EP or BEP [177].

The cure rates for testicular cancer are high, even when cancer is at an advanced stage at the time of diagnosis [177]. The overall five-year survival for testicular cancer (all stages) is 95.2% [190].

Follow-Up

Men who have been treated for testicular cancer should be followed up at regular intervals to monitor for signs of recurrence. Follow-up visits typically include a history and physical examination and serum tumor markers. The ASCO guideline on the serum tumor markers for male individuals with germ cell tumors notes that there is insufficient evidence to determine whether monitoring tumor markers improves survival or health outcomes but nonetheless recommends measuring AFP and beta-hCG levels during each surveillance visit, and the NCCN also recommends an LDH as part of surveillance [194]. Evidence is also lacking regarding optimal surveillance intervals, and the intervals vary according to diagnosis (seminoma or nonseminoma) and stage of disease [177]. In general, the recommended intervals are every two months in the first year, every three months in the second year, every six months in the third and fourth years, and annually thereafter [177]. It is recommended that surveillance continue for at least 10 years [177; 194]. Chest x-ray and computed tomography of the abdomen and pelvis are recommended at greater intervals [177].

The follow-up evaluation plays an important role in assessing for the long-term effects of treatment. The primary effect of chemotherapy is oligospermia, but sperm production can be recovered [195; 196]. A population-based study found that 70% of testicular cancer survivors fathered children [197]. Secondary acute leukemias have been reported to develop after chemotherapy and radiation therapy, and other consequences of platinum-based chemotherapy include hearing deficits and impaired renal function [198; 199]. Melanomas and cancers at many sites have been associated with radiation therapy, occurring 10 years or more after treatment [198]. Lastly, the risk of cardiac events has been increased for testicular cancer survivors who had been treated with radiation therapy and/or chemotherapy [200].

MALE BREAST CANCER

Breast cancer in men is rare; an estimated 2,710 new cases will be diagnosed in the United States in 2022, and an estimated 530 men will die of the disease [16]. These figures represent less than 1% of all breast cancer diagnosed in this country. Although the numbers are low, the prevalence has increased 26% since the early 1980s, prompting increased attention and highlighting the need to emphasize to men—and their healthcare providers—that breast cancer is not confined to women [201]. The lack of awareness of the disease has led to a longer time between the development of symptoms and diagnosis and to a later age (mean age: 67 years) and stage of disease at the time of diagnosis compared with women [201; 202].

Male breast cancer has not been extensively studied, and research is difficult because of the small numbers of men with the disease. Reviews of the literature have been helpful in identifying risk factors, clinical and pathologic characteristics, and the role of genetics [201; 202; 203]. Studies have shown that male breast cancer differs from female breast cancer in many ways. For example, some risk factors unique to men include the following [203]:

- Undescended testes
- Orchiectomy
- Infertility
- Gynecomastia
- Mastitis
- Breast trauma
- Infertility
- Klinefelter syndrome
- Radiation to the chest wall

BRCA2 mutation is found in approximately 4% to 16% of men with breast cancer [203].

A painless subareolar lump or swelling is the most common presenting symptom, occurring in approximately 85% of men with breast cancer [201; 204]. Other common symptoms are nipple retraction, localized pain, or nipple ulceration, bleeding, or discharge. About 1% to 2% of men will have no symptoms [201; 204]. In diagnosing male breast cancer, the primary consideration is to distinguish cancer from gynecomastia, which is present in about 30% of healthy men [202].

The approach to the diagnostic evaluation of male breast cancer is the same as for female breast cancer. A history and physical examination will help determine potential risk factors and identify the clinical features. Mammography has good sensitivity and specificity, and ultrasonography may be useful, especially for detecting involvement of the lymph nodes [202]. Biopsy is essential for elucidating the pathologic characteristics. In male breast cancers, the overexpression of estrogen receptor and progesterone receptors is likely [203; 205].

As noted, data on male breast cancer are limited, and recommendations for treatment have been extrapolated from the literature on female breast cancer and from small series of men with the disease. Modified radical mastectomy is used most often, with lumpectomy rarely performed [203]. Sentinel node biopsy has also been effective in men [206; 207]. Adjuvant radiation therapy has been associated with a lower local recurrence rate and a higher survival rate [202; 203]. Adjuvant chemotherapy has been carried out according to guidelines for women at high risk for recurrence. Adjuvant hormone therapy has a clear role in the treatment of men with hormone receptor-positive cancer, with reductions in recurrence and death [204; 208]. In addition, tamoxifen has led to a 50% response rate for metastatic breast cancer [202].

Five-year survival rates for men with breast cancer have been reported to be between 40% and 65% [201; 202]. In one retrospective study, the median survival was 87 months (83 months for men with invasive disease) [203]. Older age, higher stage of disease, and increasing tumor size have been associated with shorter survival [203]. The risk of second cancers (breast and nonbreast) appears to be high [209].

MALE SEXUAL HEALTH

Sexual dysfunction affects more than a quarter of men, yet attention to sexual health is low because of the lack of validated evidence-based guidelines for diagnosis and treatment as well as men's hesitancy to discuss sexual health issues with their primary healthcare providers [210; 211]. Clinicians should include questions about sexual function in routine health evaluations and foster an environment of trust and open dialogue to help elicit information on sexual health from their male patients.

Issues related to sexual health change over the course of a man's lifetime. Early ejaculation is of concern to men across the ages, erectile dysfunction and late-onset hypogonadism are of special concern to older men, and infertility and STIs are more common issues among younger men.

PREMATURE EJACULATION

The AUA definition of premature ejaculation is "poor ejaculatory control, associated bother, and ejaculation within about two minutes of initiation of penetrative sex that has been present since sexual debut" [354]. This definition and others have not been evidence based, however, and the International Society of Sexual Medicine charged a panel of experts with developing an evidence-based definition. According to this definition, premature ejaculation is "a male sexual dysfunction characterized by ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration, and the inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy" [213]. The definition is limited to men with lifelong premature ejaculation and those for whom the condition is not caused by another physical, mental, or psychological health condition. Some have called for the condition to be called "early" ejaculation as a more accurate description of the condition [214].

Premature ejaculation is thought to be the most common sexual disorder among men, and the condition is associated with a high rate of psychosocial distress and has a substantial impact on men's relationships with their partners [215; 216].

Prevalence

The reported prevalence of premature ejaculation in the United States has varied widely, ranging from 5% to 40%, depending primarily on the definition [210; 212]. The highest prevalence is found among men who are 60 years of age or older [214].

Diagnosis

There are no established criteria for the diagnosis of premature ejaculation; clinicians should assess medical, relationship, and sexual history and perform a focused physical examination to make the diagnosis [354]. Laboratory studies or physiologic testing is needed only if the history or physical examination suggests a complex cause [212; 354]. Among the details to be elicited from the history are [212]:

- Frequency and duration of premature ejaculation
- Relationship of premature ejaculation to specific partners
- Degree of stimulus resulting in premature ejaculation
- Nature and frequency of sexual activity (foreplay, masturbation, intercourse, use of visual cues)
- Impact of premature ejaculation on sexual activity

AUA RECOMMENDED PHARMACOLOGIC THERAPY OPTIONS FOR PREMATURE EJACULATION		
Agent	**Daily Dose[a]**	**Pre-Intercourse Dose (On Demand)**
Nonselective serotonin reuptake inhibitor		
Clomipramine (Anafranil)	12.5–50 mg	25–50 mg (4 to 24 hours prior to sexual activity)
Selective serotonin reuptake inhibitors		
Fluoxetine (Prozac)	5–20 mg	—
Paroxetine (Paxil)	10 mg, 20 mg, or 40 mg	20 mg (3 to 4 hours prior to sexual activity)
Sertraline (Zoloft)	25–200 mg	50 mg (4 to 8 hours prior to sexual activity)
Topical agent		
Lidocaine/prilocaine cream (EMLA cream)	—	Lidocaine 2.5%/prilocaine 2.5% (20 to 30 minutes prior to sexual activity)
[a]The lowest dose should be used when beginning therapy, with upward titration based on response.		
Source: [212; 354]		*Table 10*

- Types and quality of personal relationships and quality of life
- Aggravating or alleviating factors
- Relationship to drug use or misuse

The patient's partner may be helpful in providing a description of the problem, and care should be taken to distinguish premature ejaculation from erectile dysfunction [212]. The AUA recommends that, for men with concomitant premature ejaculation and erectile dysfunction, erectile dysfunction should be treated first [212].

According to the Male Training Center for Family Planning and Reproductive Health, asking men about problems with sexual function is particularly important to identify underlying cardiovascular disease among men who present with symptoms of sexual dysfunction routinely starting at 25 years of age. Specific questions include if the man is experiencing sexual dysfunction such as inability to obtain and maintain an adequate erection for satisfactory sexual activity (impotence, erectile dysfunction), premature or delayed ejaculation, loss of libido, painful intercourse, and also priapism, a prolonged painful erection not associated with sexual desire.

(https://rhntc.org/sites/default/files/resources/mtc_male_prevrhc_2014.pdf. Last accessed June 6, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

Treatment Options

The treatment approaches for premature ejaculation include psychologic, behavioral, and pharmacologic therapies, and the risks and benefits of all options should be discussed with the patient and, when possible, his partner [212; 354]. Behavioral therapy was once considered to be the standard therapy, but studies have shown that the best approach may involve a combination of therapies to address the limitations of each approach as well as the multimodal causes of premature ejaculation [210; 217; 218]. The 2022 AUA/Sexual Medicine Society of North America guideline recommends that, in addition to pharmacologic treatment, providers consider referring men with premature ejaculation to a mental health professional with expertise in sexual health [354].

No medication has been approved for the treatment of premature ejaculation, leaving the pharmacologic treatment to involve the off-label use of serotonin reuptake inhibitors or topical anesthetics that act by prolonging the latency of ejaculation [210; 212; 218; 219; 354]. The recommended first-line pharmacotherapeutic options are "on demand" clomipramine; a nonselective serotonin reuptake inhibitor; daily selective serotonin reuptake inhibitor (e.g., fluoxetine, paroxetine, sertraline); and topical penile anesthetics [212; 354]. The doses studied have varied, and dosing is prescribed as either continuous (daily regimen) or situational (taken only before sexual activity); the optimal duration of therapy has not been determined (***Table 10***) [212; 354]. The side effects of these drugs have not been evaluated outside the depression setting, but the effects appear to be similar for men who are not using the drug for depression, with the most common effects being nausea, dry mouth, and drowsiness [212].

Treatment with topical lidocaine/prilocaine has also been shown to be effective in increasing the latency of ejaculation and is another option recommended by the AUA [212; 220; 221]. The drug is typically applied 20 to 30 minutes before sexual activity; earlier application (30 to 45 minutes prior to sexual activity) has led to numbness of the penis and loss of erection in a substantial number of men [221]. Topical treatment avoids adverse events associated with systemic therapy [222]. In 2016, the European Union approved a topical eutectic lidocaine/prilocaine metered-dose spray (Fortacin) for use in the treatment of primary premature ejaculation [223; 224]. The spray has not been approved for this use in the United States [225].

One drug, dapoxetine, a short-acting selective serotonin reuptake inhibitor, is the first drug developed specifically for premature ejaculation, and it has been approved for use in several European countries, but not in the United States or Canada [222]. Several studies and systematic reviews have shown dapoxetine to substantially improve (compared with placebo) intravaginal ejaculatory latency time, perceived control, and patient-reported global impression of change and decrease related personal distress and difficulty [222; 226; 227; 228]. However, the agent is characterized by discontinuation rates of up to 90%, primarily due to side effects, cost issues, efficacy below expectations, and the need for scheduling sexual intercourse [224]. The most common side effects have been nausea, dizziness, diarrhea, insomnia, and headache.

Psychological and behavioral therapies are valuable components of treatment [210; 217; 218]. Relationship counseling and sex therapy can help facilitate communication between the patient and his partner and ease tension surrounding sexual activity. Psychologic and behavioral therapies should focus on gaining confidence, learning control techniques, lessening performance anxiety, overcoming barriers to intimacy, achieving pleasure, and gaining satisfaction [210; 217].

ERECTILE DYSFUNCTION

Erectile dysfunction can be conceptualized as an impairment in the arousal phase of sexual response and is defined by the AUA as "the consistent or recurrent inability to attain or maintain penile erection sufficient for sexual satisfaction, including satisfactory sexual performance" [355]. Erectile dysfunction is primarily a vascular disorder, but hormonal, neurologic, and psychologic factors are also involved. Approximately 70% of cases are organic and not of psychologic origin [229]. The term erectile dysfunction has come to replace "impotence" to more accurately describe a condition that is not associated with a loss of sexual desire or problems with ejaculation or orgasm [230].

Prevalence

Erectile dysfunction is estimated to affect 50 million men in the United States and more than 150 million men worldwide [231]. The prevalence has ranged from 10% to 30% among men 40 to 49 years of age and from 25% to 76% among men older than 70 years of age [232; 233; 234]. Ethnicity has also been a factor, with a higher rate for Black men and a lower rate for Hispanic men compared with White men [232]. However, another study showed that Hispanic men were more likely to report erectile dysfunction [234].

Erectile dysfunction has been reported to be more common among men with comorbidities; independent risk factors include age, diabetes, metabolic syndrome, cardiovascular disease, obesity, and sedentary lifestyle [214; 234; 235]. Among men with no known cardiovascular disease, erectile dysfunction has preceded coronary artery disease, stroke, and peripheral artery disease by an average of three years (range: two to five years) [236]. In addition, a meta-analysis (14 cohort studies; 92,757 men) showed that erectile dysfunction was an independent risk factor for cardiovascular and cerebrovascular events [237]. Other risk factors for erectile dysfunction include hormone disorders, neurologic conditions, psychologic disorders, history of surgery or radiation in the pelvic region, use of illicit drugs, and some prescription drugs (most notably, antihypertension agents) [238]. Encouraging men with these risk factors to modify their lifestyle and/or treating comorbidities may help reduce the risk of erectile dysfunction [239].

Diagnosis

A detailed medical history is integral to diagnosing erectile dysfunction, as the history may elucidate an underlying cause. It is important to also document a psychosocial and sexual history to evaluate the potential of other related or contributing factors [230]. The physical examination should involve assessment of the abdomen, genitals, and pulses in the lower extremity [230]. Validated questionnaires are recommended to assess the severity of erectile dysfunction, to measure treatment effectiveness, and to guide future management [355]. A morning serum total testosterone should be measured routinely; selected laboratory studies to consider are fasting glucose and serum lipid profile, hemoglobin A1c, and thyroid function tests [355].

Treatment Options

Erectile dysfunction is best managed with a combination approach [235]. Because of the strong relationship between erectile dysfunction and modifiable risk factors, lifestyle changes should be a first-line approach to managing the condition. The importance of achieving or maintaining a healthy body mass index, increasing exercise, and smoking cessation should be emphasized, especially given the relationship between erectile dysfunction and cardiovascular disease.

After treatment of erectile dysfunction is initiated, referral to a mental health professional should be considered to promote treatment adherence, reduce performance anxiety, and integrate therapies into a sexual relationship [355]. Both the AUA and the ACP recommend oral phosphodiesterase-5 inhibitors as first-line pharmacotherapy for erectile dysfunction in men for whom this class of drugs is not contrain-

dicated [230; 231; 355]. Four drugs in the class have been approved for use in the treatment of erectile dysfunction: sildenafil (Viagra), tadalafil (Cialis), vardenafil (Levitra), and avanafil (Stendra, Spedra). Sildenafil and vardenafil differ from tadalafil with respect to the time to maximum serum level (1 hour vs. 2 hours) and serum half-life (4 hours vs. 18 hours) [230]. Furthermore, the duration of action is longest for tadalafil (up to 36 hours) [240]. The inhibitory effect of these drugs causes vascular smooth muscle relaxation in the corpus cavernosum, resulting in increased erection hardness and prolonged duration in men with erectile dysfunction who have sufficient intact vasculature [355].

Data from multiple trials and systematic reviews have demonstrated similar efficacy for phosphodiesterase-5 inhibitors in treating erectile dysfunction, particularly for sildenafil, tadalafil, and vardenafil [355]. Each of these drugs substantially improves erectile function and successful sexual intercourse compared with placebo [231]. Relative efficacy is less clear for avanafil because published comparative studies are limited. The ACP notes that there is insufficient evidence for recommending one drug over another and suggests that the choice be made according to the preferences of an individual patient with respect to ease of use, cost, and the adverse effects profile [231]. One systematic review and meta-analysis found evidence that tadalafil is the most effective agent, followed by vardenafil, with no major differences in the safety profile of any of the phosphodiesterase-5 inhibitors [241].

The side effects of all four drugs are similar, with headache, dyspepsia, facial flushing, nasal congestion, and visual disturbances being the most common events [230; 240; 242]. The FDA has issued two mandates to revise labeling of these agents. In 2005, the agency required labels for sildenafil, tadalafil, and vardenafil to reflect the possibility of sudden vision loss after taking the drugs for a period of time [243]. The alert was associated with several case reports suggesting a temporal association between use of one of the drugs and nonarteritic anterior ischemic optical neuropathy (NAION), a rare disorder characterized by sudden loss of vision in one eye [243; 355]. However, subsequent studies showed that the risk of NAION was similar among men who were and were not taking a phosphodiesterase-5 inhibitor [244; 245]. Risk factors for spontaneous NAION include older age, White race, small optic discs with low cup-to-disc ratio, and vascular disease, leading some investigators to suggest an examination of the fundus be performed on men who may be at higher risk for NAION before a phosphodiesterase-5 inhibitor is prescribed [243].

In 2007, the FDA mandated changes to the labels of phosphodiasterase-5 inhibitors to more prominently display warnings about the potential for sudden hearing loss [246]. A cross-sectional population-based study of more than 11,000 men subsequently demonstrated a higher likelihood of self-reported hearing loss associated with use of any phosphodiasterase-5 inhibitor (odds ratio: 2.23), but the association was significant only for sildenafil [247].

Use of a phosphodiesterase-5 inhibitor is contraindicated in several situations. They should not be taken by men who take organic nitrates (nitroglycerin) or nitrites (amyl nitrite) [248; 249]. Vardenafil should not be used for men with a history of prolonged QT interval (or who take medication to prolong the QT interval) [230]. The use of a phosphodiesterase-5 inhibitor concomitantly with an alpha-blocker for lower urinary tract symptoms may lead to increased systemic vasodilation and hypotension [230].

Men who are being treated with a phosphodiesterase-5 inhibitor should be followed up closely to monitor efficacy and side effects. Attention to changes in health status and other medications is essential to avoid drug interactions. Clinicians should emphasize the importance of men providing information about treatment with a phosphodiesterase-5 inhibitor in case of a cardiovascular emergency [230].

Although the initial treatment option preferred by most men with erectile dysfunction is a phosphodiesterase-5 inhibiter, the AUA Panel notes that it is valid for men to begin with any type of established treatment, and recommends that patients be informed of all treatment options that are not medically contraindicated. The AUA guideline provides data on success rates, patient and partner satisfaction rates, and potential adverse effects for the following treatment options [355]:

- Vacuum erection device: An effective, low-cost option with high rates of patient and partner satisfaction. May have a role as "rescue device" or adjunct to pharmacologic therapy.
- Intraurethral alprostadil: Involves insertion of a delivery catheter into the urethral meatus and depositing an alprostadil tablet in the urethra; requires an in-office trial to insure effectiveness and safety. Variable rates of success (30% to 78%).
- Intracavernosal injection: Administered by injecting medication (i.e. alprostadil) into the corpus cavernosa of the penis to produce an erection; an in-office injection test should be performed. Reported success rates range from 58% to 100%.
- Penile prosthesis implantation: Surgical procedure that requires thorough patient and partner counselling. Available devices include malleable (non-inflatable) models as well as inflatable prostheses. Satisfaction rates vary across models, ranging from 66% to 88%.

Intracavernosal injection of a vasoactive drug is associated with the highest potential for priapism, and clinicians should ensure that men understand the correct technique and the importance of seeking medical intervention for a prolonged erection [230]. Only vacuum erection devices with a limiter (a feature that limits the amount of vacuum pressure and reduces potential for penile injury) should be recommended, whether purchased over the counter or procured by prescrip-

SYMPTOMS AND SIGNS SUGGESTIVE OF TESTOSTERONE DEFICIENCY IN MEN	
Specific	Incomplete or delayed sexual development, eunuchoidism Loss of body (axillary and pubic) hair, reduced shaving Very small (especially <5 mL) or shrinking testes
Suggestive	Reduced sexual desire (libido) and activity Decreased spontaneous erections Breast discomfort, gynecomastia Inability to father children, low or zero sperm count Height loss, low trauma fracture, low bone mineral density Hot flushes, sweats
Nonspecific	Decreased energy, motivation, initiative, and self-confidence Feelings of sadness or being "blue," depressed mood, dysthymia Poor concentration and memory Sleep disturbance, increased sleepiness Mild unexplained anemia (normochromic, normocytic, in the female range) Reduced muscle bulk and strength Increased body fat, body mass index

Source: Modified, with permission, from Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2018;103(5):1715-1744. *Table 11*

POTENTIAL BENEFITS AND RISKS OF TESTOSTERONE THERAPY	
Benefits	**Potential Risks**
Improvement in sexual desire and function	Stimulation of growth of prostate cancer
Increase in bone mineral density	Worsening of symptoms related to benign prostatic hypertrophy
Improvements in mood, energy, and quality of life	Liver toxicity and liver tumor
Change in body composition and improvement in muscle mass and strength	Gynecomastia
Improvement in cognitive function	Erythrocytosis Testicular atrophy and infertility Skin diseases Sleep apnea

Source: [262] *Table 12*

tion [230; 355]. The AUA advises that for men with erectile dysfunction, low-intensity extracorporeal shock wave therapy and intracavernosal stem cell therapy are considered investigational treatment options [355]. The risks associated with penile prostheses include mechanical failure, erosion, and infection [230]. The AUA guideline does not recommend the use of trazodone, testosterone therapy (for men with normal serum levels), or yohimbine and other herbal therapies [230].

Psychosocial therapy is an important component of treatment for erectile dysfunction. A meta-analysis showed that group psychotherapy in combination with sildenafil significantly improved erectile function and successful sexual intercourse compared with sildenafil alone [250].

LATE-ONSET HYPOGONADISM

In both men and women, levels of sex hormones decline with age. However, the ways in which these levels change and the symptoms associated with the decline differ greatly between men and women. There is no well-defined equivalent of menopause in men, although the phrase "andropause" is used frequently to refer to decreased testosterone and resulting symptoms. Other phrases, most notably androgen deficiency syndrome and late-onset hypogonadism, may be more accurate descriptors of the process. By any name, the condition is a complex of symptoms that includes loss of sexual satisfaction and overall well-being [251]. The condition is related to lower testosterone levels, which begin to decrease 1% to 2% each year beginning at 30 years of age [252].

RECOMMENDATIONS OF THE ENDOCRINE SOCIETY REGARDING TESTOSTERONE THERAPY FOR ADULT MEN WITH HYPOGONADISM	
Diagnosis and evaluation	*Recommendations* Make a diagnosis of hypogonadism only in men with symptoms and signs consistent with testosterone deficiency and unequivocally and consistently low serum testosterone levels and/or free testosterone concentrations (when indicated). Confirm diagnosis by repeating measurement of fasting morning total testosterone. Measure serum luteinizing hormone and follicle-stimulating hormone levels to distinguish between primary (testicular) and secondary (pituitary-hypothalamic) hypogonadism. *Suggestions* Perform further evaluation to identify the etiology of hypothalamic, pituitary, and/or testicular dysfunction in men with hypogonadism. Measure serum testosterone level in men who have specific clinical signs and symptoms and consider measuring serum testosterone level in men who report less specific signs and symptoms. Measure morning total testosterone level by a reliable assay as the initial diagnostic test. Measure free or bioavailable testosterone level, using an accurate and reliable assay, in men in whom total testosterone concentrations are near the lower limit of the normal range and in whom alterations of sex hormone-binding globulin are suspected. Do not evaluate androgen deficiency during an acute or subacute illness. Measure bone mineral density with use of dual-energy x-ray absorptiometry scanning in men with severe androgen deficiency or low trauma fracture.
Treatment	*Recommendations* Use testosterone therapy for men with hypogonadism to induce and maintain secondary sex characteristics and correct symptoms of testosterone deficiency. Do not use testosterone therapy for men planning fertility in the near term or in men with breast or prostate cancer. Do not use testosterone therapy without further urologic evaluation in men with palpable prostate nodule or induration or a prostate-specific antigen (PSA) level of 3 or 4 ng/mL in men at high risk of prostate cancer (e.g., Black race, first-degree relative with prostate cancer). Do not use testosterone therapy for men with a hematocrit greater than 50%, untreated severe obstructive sleep apnea, severe lower urinary tract symptoms, or uncontrolled or poorly controlled heart failure, or in men with type 2 diabetes (as a means of glycemic control) who have low testosterone concentrations. *Suggestions* Initiate testosterone therapy with any of the following regimens, chosen on the basis of an individual man's preference, consideration of pharmacokinetics, treatment burden, and cost: • Testosterone enanthate or cypionate: 75–100 mg IM weekly, or 150–200 mg IM every two weeks • Testosterone patch (nongenital): 5 mg, one or two applied nightly over the skin of the back, thigh, or upper arm (away from pressure areas) • Testosterone gel (1%): 5–10 g applied daily over a covered area of nongenital skin • Testosterone bioadhesive buccal tablet: 30 mg applied to buccal mucosa every 12 hours • Testosterone pellets: SC every three to six months (dose and regimen vary with the formulation used) • Oral testosterone undecanoate, injectable testosterone undecanoate, testosterone-in-adhesive matrix patch, and testosterone pellets, where available Consider short-term testosterone therapy in men with HIV, low testosterone concentrations, and weight loss (when other causes of weight loss have been excluded) to induce and maintain body weight and lean mass gain. Do not routinely prescribe testosterone therapy to all men 65 years of age or older with low testosterone concentrations. Offer testosterone therapy on an individualized basis after discussing the risks/benefits with the patient.
Monitoring	*Recommendations* Evaluate the patient three to six months after the initiation of treatment and then annually. Determine hematocrit at baseline, at three to six months, and then annually. (Stop therapy if the hematocrit is higher than 54%.) Evaluate the patient for signs and symptoms of formulation-specific adverse events at each visit. Obtain a urologic consultation if there is any of the following: • Increase in serum or plasma PSA level >1.4 ng/mL within any 12-month period of testosterone treatment • PSA velocity >0.4 ng/mL/yr using the PSA level after 6 months of testosterone therapy as the reference (PSA velocity should be used only if there are longitudinal PSA data for more than two years.) • Detection of a prostatic abnormality on digital rectal examination • AUA/IPSS score >19 *Suggestions* Monitor testosterone levels three to six months after initiation of testosterone therapy, with an aim of achieving serum testosterone levels during treatment in the mid-normal range. (For men receiving testosterone enanthate or cypionate, the aim should be a testosterone level between 350 and 600 ng/dL at one week after the injection.) Repeat bone mineral density of the lumbar spine, femoral neck, and hip after one to two years of testosterone therapy in hypogonadal men with osteoporosis or low trauma fracture.
Screening	*Recommendation* Do not screen for hypogonadism in the general population.

Source: [252] *Table 13*

Late-onset hypogonadism is distinct from hypogonadism in younger male individuals. For boys and young men, hypogonadism is related to testicular failure and is usually associated with a congenital abnormality, most often Klinefelter syndrome [251]. In older men with hypogonadism, testosterone levels are rarely as low as the levels in young men with primary hypogonadism [251].

Several important questions about late-onset hypogonadism remain unanswered [252; 253]:

- It is unclear whether the symptoms are caused by a reduction in testosterone or are a result of the normal physiologic process of aging.
- There is no consistent level of testosterone to define hypogonadism, and there is confusion about what testosterone levels should be measured.
- There is ongoing debate about the risk-benefit ratio of testosterone therapy for older men.

Prevalence

There is a wide range in the reported prevalence of late-onset hypogonadism. In a population-based observational study, symptomatic androgen deficiency was found in nearly 6% of men 30 to 79 years of age, whereas in the Hypogonadism in Males (HIM) study, the prevalence was nearly 39% among men 45 years of age and older visiting primary care practices [254; 255]. The prevalence increases substantially with age and is similar across racial/ethnic populations [254; 255].

Diagnosis

A diagnosis of late-onset hypogonadism requires both documentation of relevant symptoms and measurement of testosterone levels. The condition is associated with a variety of physiologic, psychologic, cognitive, and sexual symptoms; some signs and symptoms are more specific than others, and no combination of symptoms is typical (***Table 11***) [252; 255].

Diagnosing late-onset hypogonadism (testosterone deficiency) is challenging because many signs and symptoms are associated with the normal process of aging or can be attributed to coexisting conditions. Two questionnaires that can help to identify late-onset hypogonadism are the Androgen Deficiency in Aging Males (ADAM) questionnaire and the Aging Males' Symptoms (AMS) scale [256; 257; 258; 259; 260]. The ADAM questionnaire consists of 10 questions, and the condition is defined by a positive response to two specific questions: "Do you have a decrease in libido (sex drive)?" and "Are your erections less strong?" or to any three of the other questions [256]. The AMS scale asks men to provide a score of 1 to 5 to each of 17 somatic, psychologic, and sexual symptoms. The ADAM questionnaire has been validated against testosterone levels, whereas the AMS scale was designed to evaluate the quality of life and has not been correlated to testosterone levels [261]. Both have excellent specificity but poor sensitivity [251].

In its updated practice guidelines on the treatment of androgen deficiency, the Endocrine Society recommends making a diagnosis of hypogonadism "in men with symptoms and signs of testosterone deficiency and unequivocally and consistently low serum testosterone and/or free testosterone concentrations (when indicated)" [252]. Serum testosterone level fluctuates in relation to time of day and food intake; peak concentrations occur during the morning hours. Therefore, clinicians should measure total testosterone concentrations on two separate mornings while the patient is fasting [252]. Measured levels should be interpreted with caution as not all laboratories use total testosterone assays harmonized to the national standard [355]. Intercurrent acute illness, nutritional deficiency, and certain medications (e.g., opioids, glucocorticoids) can alter the expected serum testosterone concentration. In general, a total testosterone concentration of 300 ng/dL is the cut-off level below which testosterone replacement therapy is considered for most men with suspected late-onset hypogonadism.

Treatment Options

The increase in treatment with testosterone has been tremendous. Although there are benefits of testosterone therapy, there are also many potential risks (***Table 12***), and the risk-benefit ratio for men with late-onset hypogonadism has not been clearly defined [255; 256; 261]. Because of questions about the benefits and harms of testosterone, the Endocrine Society is specific in its recommendations for testosterone therapy (***Table 13***) and recommends against a general policy of offering testosterone therapy to all older men with low testosterone levels [252].

Testosterone replacement is available in several forms, including oral agents, injectable formulations, transdermal gels and patches, and buccal tablets [252; 263]. In general, a decision on the type of therapy should be made according to the patient's preference, with consideration of several factors, including pharmacokinetics, cost, ease of use, and side effect profile [252; 263].

Follow-Up

Close follow-up is essential for men being treated with testosterone replacement. The clinical response and side effects should be monitored at intervals of three to six months [252]. The treatment target should be a testosterone level in the middle of the normal range [252]. Follow-up should include evaluation of the prostate, through determination of PSA levels and DRE at three to six months for men 40 years of age and older who have a baseline PSA greater than 0.6 ng/mL. In addition, a hematocrit level should be determined at three to six months and then annually; treatment should be discontinued if the hematocrit is greater than 54%.

MALE INFERTILITY

Infertility is clinically defined as the inability to conceive after one year of unprotected intercourse [264]. Approximately 15% of couples are unable to conceive after one year of unprotected intercourse. A male factor is the only cause in approximately 20% of infertile couples and is a contributing factor in another 20% to 40% [264]. Fertility declines with age, and research has shown that men older than 35 years of age are twice as likely to be infertile as men younger than 25 years of age [265; 266]. Approximately 15% of infertile men have azoospermia, the complete absence of sperm in the ejaculate [267].

Etiology

More than half of male infertility or subfertility is potentially correctable; often, the cause is unknown. The causes, both correctable and uncorrectable, include [264; 268]:

- Varicocele
- Obstruction of a duct (epididymal, vasal, or ejaculatory)
- Ejaculatory dysfunction
- Testicular atrophy
- Hypogonadotropic hypogonadism
- Infection
- Side effects of medication
- Environmental toxins
- Bilateral cryptorchidism
- Genetic abnormality (Y chromosome microdeletion)
- Congenital absence of vas deferens

Diagnosis

According to the AUA guidelines, evaluation of suspected male infertility should include a complete medical and reproductive history, physical examination, and one or more semen analyses [264; 356]. Men with one or more abnormal semen parameters or presumed male infertility should be evaluated by a male reproductive expert. It is important not to rely solely on semen analysis, as an underlying medical or genetic cause of infertility may be missed [268]. Other tests may be necessary, depending on the findings of this initial evaluation. Clinicians should obtain hormonal evaluation including follicle-stimulating hormone (FSH) and serum testosterone for infertile men with any of the following: impaired libido, erectile dysfunction, oligozoospermia or azoospermia, atrophic testes, or evidence of hormonal abnormality on physical examination [356].

The medical history can help to detect an underlying cause of infertility. Factors that can affect fertility include [268]:

- Kallmann, Young, or Kartagener syndrome
- Pituitary disease
- Previous testicular disorders
- History of inguinal, scrotal, or retroperitoneal surgery
- Anticancer chemotherapy

The reproductive history should address the following issues: frequency and timing of intercourse, duration of fertility effort, use of lubricants, and sexual history (including STIs) [264; 267; 268].

Physical examination may identify a varicocele, the most common cause of male infertility [165; 182]. Other findings on physical examination that may suggest a cause of infertility include small testes (less than 4 cm in greatest dimension or less than 20 cm3), signs of ductal obstruction (induration or engorgement of the vas deferens or epididymis), and abnormal distribution of hair and fat, which may indicate endocrinopathy [268].

As noted, the semen analysis should be carried out on at least two specimens, obtained at least one month apart [264]. The specimens should be collected after two to three days of abstinence. The World Health Organization (WHO) first established reference values for semen analysis in 1987 and published its sixth update in 2021 [269]. The 2020 AUA guideline references the 2010 WHO semen parameters and lower reference limit criteria for male infertility [356]:

- Semen volume: 1.5 mL
- Total sperm number: 39 million/ejaculate
- Sperm concentration: 15 million/mL
- Vitality: 58% live
- Total motility (progressive + nonprogressive): 40%
- Morphologically normal forms: 4.0%

Initially, the updated criteria met with controversy, with some noting that the new reference values would lead to fewer men being classified as infertile based on semen analysis alone [271; 272; 356]. No single abnormality among sperm parameters is diagnostic of infertility; the odds ratio for infertility increases with the number of abnormal semen parameters, rising sharply with two or more abnormal parameters [356].

Treatment Options

Treatment options are available for correctable causes of infertility. Varicoceles can be repaired through open or laparoscopic surgery or by percutaneous embolization [182]. Surgical treatment leads to elimination of the varicocele in 90% of men, with improvement in the semen quality, production of testosterone, and rates of subsequent pregnancy [182; 273]. For men with infertility related to obstruction, microsurgical reconstruction of the obstructed duct has led to the appearance of sperm in the ejaculate and higher rates of subsequent pregnancy [267]. Several techniques for retrieving sperm are also available. Options for reproductive assistance and adoption should be explored for men who have uncorrectable infertility. Genetic counseling should be offered to men with nonobstructive azoospermia due to primary testicular failure [267].

RATE OF COMMON SEXUALLY TRANSMITTED INFECTIONS (STIs) AMONG MEN ACCORDING TO RACE/ETHNICITY, 2020							
STI	Prevalence (per 100,000)						
	All Men	Black (Non-Hispanic)	American Indian/ Alaskan Native	Hispanic	White (Non-Hispanic)	Asian	Native Hawaiian/ Other Pacific Islander
Chlamydia	336.7	883.7	315.8	198.0	113.2	72.0	300.6
Gonorrhea	236.3	819.5	272.3	144.8	77.4	46.6	195.8
Syphilis (primary and secondary)	20.7	57.7	32.6	23.4	11.0	8.9	30.7
Source: [57]							*Table 14*

EVIDENCE-BASED PRACTICE RECOMMENDATION

The National Collaborating Centre for Women's and Children's Health recommends that men be informed that there is an association between elevated scrotal temperature and reduced semen quality, but that it is uncertain whether wearing loose-fitting underwear improves fertility.

(https://www.nice.org.uk/guidance/cg156. Last accessed June 6, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

SEXUALLY TRANSMITTED INFECTIONS

STIs are a serious public health concern. There are an estimated 26 million new infections annually and 68 million total STIs in the United States, of which youth 15 to 24 years of age account for about half [357]. In addition to the substantial morbidity associated with STIs, the financial cost is tremendous; nearly $16 billion in direct medical costs annually are associated with the eight major STIs (chlamydia, gonorrhea, hepatitis B virus, HIV, human papillomavirus [HPV], herpes simplex virus type 2 [HSV-2], trichomoniasis, and syphilis) [275]. The large majority of costs are attributable to HIV ($13.7 billion), followed by chlamydia ($691 million), gonorrhea ($271 million), and HSV-2 ($91 million) [57].

The discussion here is confined to STIs having the greatest impact on men: chlamydia, gonorrhea, syphilis, HSV-2, and HPV [57]. Although HSV-2 and HPV infections are more common among women than men, the infections have serious implications for men. For example, nearly one-third of the 22,000 HPV-associated cancers that occur each year in the United States develop in men [276]. Infection with HSV-2 increases the risk for HIV, which is particularly important for Black men, who are at greater risk for both HSV-2 and HIV [277].

Despite the availability of comprehensive guidelines for the testing and treatment of STIs, studies have shown poor compliance; in one study, fewer than one-third of individuals with an STI seen in an emergency department received recommended antibiotic treatment, and compliance with history-taking, diagnostic testing, and counseling ranged from 14% to 79% [278]. In addition, improvements in rates of HPV vaccination are needed [279].

Prevalence of STIs

The prevalence of STIs according to gender vary with infection; chlamydia, HSV-2, and HPV occur more often among female than male individuals; gonorrhea occurs at similar rates among female and male individuals; and syphilis occurs more often among male than female individuals [57; 277; 280]. Overall, almost two-thirds of all STIs occur in individuals 15 to 24 years of age [57]. Among men, most STIs are far more prevalent in the non-Hispanic Black population than in other ethnic/racial populations and are least prevalent in the Asian population (***Table 14***) [57; 277; 281].

Chlamydia

More than 1.5 million cases of chlamydia were reported to the CDC in 2020 [57]. The 2020 rate of chlamydia infection (481.3 cases per 100,000) represents a decrease of 13% over the rate in 2019. During 2019–2020, rates of reported chlamydia decreased among both men and women. Chlamydial infection occurs more than twice as commonly in women than men, and rates are highest among adolescents and young adults.

Gonorrhea

In 2020, a total of 677,769 cases of gonorrhea were reported to the CDC, making it the second most commonly reported notifiable sexually transmitted disease in the United States [57]. Rates of gonorrhea have increased 111% since the historic low of 98.1 cases per 100,000 in 2009. In 2020, the rate of gonorrhea among men was 236.3 cases per 100,000, compared with 150 cases per 100,000 among women [57].

Syphilis

In 2000–2001, the rate of syphilis (primary and secondary) was 2.1 cases per 100,000; however, the rate has increased almost every year since that time, increasing 6.8% between 2019 and 2020 [57]. In 2020, 133,945 cases of syphilis were reported, including 41,655 cases of primary and secondary syphilis, the most infectious stages of the disease. Rates of syphilis have increased in most racial/ethnic groups, with greatest increases among non-Hispanic American Indian/Alaska Native persons and non-Hispanic persons of multiple races [57]. Young men who have sex with men are disproportionally impacted, accounting for a majority (53%) of all male syphilis cases in 2020 [57].

HSV-2

Genital herpes is a chronic, lifelong viral infection; the prevalence is unknown as the majority of persons infected have not had the condition diagnosed. Many individuals with HSV-2 have mild symptoms or unrecognized infection but shed the virus intermittently in the urogenital area. Consequently, most genital infections are transmitted by persons unaware that they have the infection. Most cases of recurrent genital herpes are caused by HSV-2, and 11.9% of persons 14 to 49 years of age in the United States are estimated to have acquired this infection [173]. In 2020, the CDC estimated the prevalence of HSV-2 at 18.6 million persons, though the actual number is likely to be considerably higher [57; 173]. The seroprevalence of HSV-2 is more than twice as high among female individuals (about 34%) than among male individuals (about 15%) [57]. As with other STIs, HSV-2 infection is more common among non-Hispanic Black men than other racial/ethnic populations [57].

HPV

Data on HPV infection in men are limited. According to a data brief published by the National Center for Health Statistics (NCHS), during 2011–2014, the seroprevalence of any HPV was 7.3% among adults 18 to 69 years of age, with 11.5% among men and 3.3% among women [282]. In the HIM study, an ongoing prospective cohort study of the natural history of HPV in men (from the United States, Mexico, and Brazil), the overall prevalence of HPV infection was 65.2%, with the highest rates among White and Black men (71.5% and 66.2%, respectively) and the lowest, among Asian/Pacific Islander men (42.2%) [281; 283]. An estimated 34,800 new HPV-attributable cancers occurred every year during 2012–2016; before introduction of HPV vaccines, approximately 355,000 new cases of anogenital warts occurred every year [173].

Prevention, Control, and Screening

Prevention and control are keys to lowering the prevalence of STIs, and the primary preventive strategies are: risk assessment, education, and counseling; limiting the number of sexual partners; abstinence or the use of condoms and barriers; and, in the case of HPV, with vaccination [173; 276]. The importance of abstaining from sexual activity should be emphasized to individuals with a confirmed STI [173].

Control of STIs involves the identification of asymptomatic individuals and of symptomatic individuals who may not seek health care; effective diagnosis and treatment; and the evaluation, treatment, and counseling of sex partners of infected individuals [173]. The CDC encourages clinicians to promote prevention with patient-centered education that focuses on risk reduction measures directed at an individual patient's personal risk [173]. Obtaining a thorough sexual history is an essential component of prevention, and the CDC suggests asking questions related to [173]:

- Partners (gender and number)
- Protection (from STIs)
- Practices (types of sexual activity)
- Past history of STIs (patient and partners)
- Prevention (of pregnancy)
- Use of injected drugs (patient and partners)
- Exchange of money for sex (patient and partners)
- Other sexual practices

Practical strategies for risk assessment and counseling are provided in the CDC treatment guidelines document [173]. Healthcare providers should use simple, direct language when asking these questions, taking care to exhibit respect, compassion, and a nonjudgmental attitude [173]. Organizations such as the National Network of STI/HIV Prevention Training Centers, a CDC-funded group, can help providers enhance skills in counseling individuals about prevention. Resources can be found on the organization's website, available at https://www.cdc.gov/std/treatment/resources.htm.

The U.S. Preventive Services Task Force recommends behavioral counseling for all sexually active adolescents and for adults who are at increased risk for sexually transmitted infections.

(https://jamanetwork.com/journals/jama/fullarticle/2769474. Last accessed June 6, 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.)

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS FOR SCREENING FOR SEXUALLY TRANSMITTED INFECTIONS (STIs) IN MALE INDIVIDUALS	
STI	**Recommendation**
Chlamydia and gonorrhea	Insufficient evidence to recommend for or against screening in men
Syphilis	Strongly recommend screening for individuals at increased risk
Genital herpes	No screening for asymptomatic adults and adolescents
Source: [284; 360; 361]	*Table 15*

Recommendations for screening vary according to risk and the type of STI (***Table 15***) [284]. The USPSTF also recommends high-intensity behavioral counseling for all sexually active adolescents and for adults at increased risk for STIs and HIV [284]. The USPSTF has not issued recommendations for screening for HPV, but beginning in 2011, the Advisory Committee on Immunization Practices (ACIP) recommended HPV vaccination for male individuals [276]. The ACIP recommends routine use of quadrivalent HPV vaccine for boys 11 or 12 years of age and for male individuals 13 to 26 years of age who have not initiated or completed the three-dose series [276; 286]. The ACIP also notes that men 27 to 45 years of age may also be vaccinated if at high risk, as determined through shared decision-making [276; 285; 286]. In addition, hepatitis B vaccination is recommended for any patient who is being evaluated for an STI [173].

Diagnosis

The symptoms of STIs vary and are often similar to symptoms associated with other conditions of the urogenital tract, and some infected individuals may be asymptomatic.

Infection with chlamydia is often asymptomatic [173]. Diagnosis can be made by testing of a urethral or rectal swab or a urine specimen [173]. Nucleic acid amplification tests are the most sensitive tests and can be used for urine specimens [173].

Primary syphilis usually presents as a solitary chancre that develops at the site of infection approximately three weeks after exposure to the spirochete *Treponema pallidum* [287]. The chancre is typically painless and must be distinguished from other genital lesions, such as genital herpes, venereal warts, chancroid, and lymphogranuloma venereum (caused by *C. trachomatis*) [287].

Dark-field microscopy to detect *T. pallidum* is the optimum method of diagnosing syphilis. Although no such detection tests are commercially available, some laboratories provide locally developed and validated polymerized chain reaction (PCR) tests for the detection of *T. pallidum* [173]. A presumptive diagnosis of syphilis can be made with two types of serologic tests: nontreponemal tests (Venereal Disease Research Laboratory [VDRL] and rapid plasma regain [RPR] tests) and treponemal tests (such as fluorescent treponemal antibody absorbed [FTA-ABS] tests or the *T. pallidum* passive particle agglutination [TP-PA] assay) [173]. The CDC notes that using only one type of serologic test is insufficient for a diagnosis [173].

Gonococcal infection, which is caused by *Neisseria gonorrhoeae* (a gram-negative diplococcus), can lead to either urethritis or epididymitis [288]. Urethritis is accompanied by such symptoms as purulent discharge from the penis, dysuria, or erythema at the meatus [288]. Epididymitis caused by gonococcal infection is usually associated with unilateral testicular pain and no other symptoms [288]. Disseminated infection is rare (1% to 3%) [289]. A diagnosis of gonorrhea is confirmed by Gram stain and culture of urethral discharge or swab specimen for *N. gonorrhoeae*, or by nucleic acid amplification testing done on a urine sample [173; 288]. Both techniques have similar sensitivity and specificity [173].

The CDC recommends that all individuals who are evaluated for gonorrhea should also be evaluated for chlamydia, syphilis, and HIV infection [173]. In one study of more than 3,800 men and women, approximately 10% to 30% of individuals with gonorrhea had concomitant infection with chlamydia [290]. The typical lesions of genital HSV-2 in men appear on or around the penis and are first noted as either a single or multiple erythematosus macular lesion(s). However, these lesions are absent in many infected individuals [173]. Viral culture is the preferred test for the diagnosis of HSV-2, but it requires two to seven days for results. The sensitivity of viral culture depends on the quality of the sample and the time at which the sample is obtained; sensitivity declines as the lesion begins to heal. A PCR test is available and is suggested by the CDC for analysis of cerebrospinal fluid when central nervous system disease is suspected [173]. Type-specific serologic tests are available as laboratory assays and point-of-care tests [173]. These tests have varying degrees of sensitivity for the detection of the HSV-2 antibody (80% to 90%) and specificity of at least 96% [173].

Treatment Options

The treatment of STIs has four main goals [173]:

- Eradicate infection
- Alleviate symptoms and signs
- Decrease complications (infertility, chronic pain, dissemination of disease)
- Prevent transmission

TREATMENT OF CHLAMYDIA, SYPHILIS, AND GONORRHEA AS RECOMMENDED BY THE CENTERS FOR DISEASE CONTROL AND PREVENTION

Infection	Recommended Treatment	Notes
Chlamydia	Doxycycline 100 mg orally twice daily for 7 days ALTERNATIVE REGIMENS Azithromycin 1 g orally in a single dose OR Levofloxacin 500 mg orally once daily for 7 days	A meta-analysis showed treatment failure among men was higher for azithromycin than for doxycycline.
Gonorrhea	Ceftriaxone 500 mg IM (single dose) PLUS Doxycycline 100 mg PO twice daily for seven days, unless chlamydia infection has been excluded	For persons weighing >150 kg, 1 g ceftriaxone should be administered. See guideline for alternative cephalosporin selection and dosing if ceftriaxone is not available.
Primary and secondary syphilis	Benzathine penicillin G 2.4 million units IM (single dose)	Additional doses do not enhance efficacy. For patients allergic to penicillin, alternative regimens include doxycycline (100 mg PO, twice daily for 14 days) or tetracycline (500 mg PO, four times daily for 14 days)

Source: [173] *Table 16*

TREATMENT OF HSV-2 AS RECOMMENDED BY THE CENTERS FOR DISEASE CONTROL AND PREVENTION

Drug	Treatment Dosage		
	Initial Infection	Episodic Recurrent Infection	Long-Term Suppression
Acyclovir	400 mg three times daily for 7 to 10 days OR 200 mg, five times daily for 7 to 10 days	800 mg two times daily for 5 days OR 800 mg three times daily for 2 days	400 mg twice daily
Famciclovir	250 mg, three times daily for 7 to 10 days	125 mg two times daily for 5 days OR 1.0 g two times (single day)	250 mg twice daily
Valacyclovir	1 g two times daily for 7 to 10 days	500 mg two times daily for 3 days OR 1.0 g once daily for 5 days	500–1,000 mg once daily

Source: [173] *Table 17*

The CDC has developed comprehensive guidelines for the treatment of STIs, last updated in 2021 (***Table 16*** and ***Table 17***) [173]. For chlamydia, gonorrhea, or syphilis, single-dose regimens generally offer an advantage for the treatment of individuals with poor healthcare-seeking or compliance behaviors [173]. The CDC notes that for the treatment of syphilis, neither combinations of benzathine penicillin and procaine penicillin nor oral penicillin preparations are considered appropriate and emphasizes the importance of distinguishing the standard benzathine penicillin product widely used in the United States (Bicillin L-A) from the combination benzathine-procaine penicillin (Bicillin C-R); the latter is not appropriate for the treatment of syphilis [173].

In addition to antibiotic treatment, bed rest, scrotal elevation, and analgesics can help to alleviate symptoms such as fever and local inflammation, which are primarily associated with gonorrhea. Beginning treatment as early as possible decreases the likelihood of complications and spread of infection, especially in the case of syphilis [173]. To prevent the transmission of infection, a patient with a confirmed or suspected STI should be told to avoid sexual contact until therapy is completed and he (and/or his partner) no longer has symptoms [173]. The need for sexual partners to be evaluated for treatment should also be emphasized. State and local health departments may provide assistance in arranging for the evaluation and treatment of sex partners of infected men.

HSV-2

The antiviral medications used to treat HSV-2 can only partially control the signs and symptoms of infection; they cannot eradicate the virus or reduce the risk, frequency, or severity of recurrence after the treatment course has been completed [173]. Men with HSV-2 infection should be given medication for episodic treatment of recurrent infection; treatment should begin within one day after the onset of a lesion [173]. If recurrences are frequent (six or more within a year), long-term suppression therapy may be appropriate; such therapy has been shown to reduce the frequency of recurrence by 70% to 80% [173].

Follow-Up

Peterman et al. found a 14.7% rate of reinfection among men during the first year after treatment for an STI [291]. An unexpected finding in the study was the high percentage (66%) of asymptomatic infections. The authors suggested that treated individuals be rescreened at three months. The CDC recommends follow-up with clinical examination and serologic evaluation at 6 and 12 months after treatment [173].

All states require that cases of chlamydia, gonorrhea, syphilis, HIV, and acquired immune deficiency syndrome (AIDS) be reported to local health authorities [173]. Clinicians should seek advice from state or local health departments if reporting requirements are unclear [173].

HEALTH ISSUES FOR MEN WHO HAVE SEX WITH MEN

It is difficult to determine an accurate percentage of MSM in the overall population because of the under-reporting of sexual behavior, but surveys indicate that this group of men represents at least 4% and up to approximately 16% of the population seen by any given healthcare professional [58; 292; 293]. The population that includes MSM (made up of gay, bisexual, and transgender individuals) has been identified as one of the six most underserved groups in the United States, yet medical training and standard resources for healthcare providers lack information on addressing the routine health concerns of this population [292; 294]. MSM have specific healthcare needs that clinicians must understand in order to provide appropriate, comprehensive care.

Perhaps the most important health risk for MSM is their avoidance of routine health care [293]. MSM do not seek routine health care for a variety of reasons. They may have difficulty coming to terms with their sexual identity, fear being judged by healthcare professionals, or be embarrassed to discuss their sexual behavior. In addition, many MSM do not recognize their health risks or their need for screening and preventive health care [58; 294]. Health risks also may not be recognized by MSM who do seek health care, and they may not be forthcoming about sexual behavior [294; 295]. A study has indicated that less than 20% of MSM had discussed their risk of HIV infection with their healthcare provider [296].

Creating a welcoming clinical environment is the first step in fostering an open dialogue between healthcare providers and MSM [240; 295]. Among the factors that contribute to such an environment are educational materials about specific healthcare needs for gay and lesbian individuals, a posted statement of nondiscriminatory care, and forms that contain more inclusive choices and gender-neutral language [240; 295]. In addition, healthcare professionals and office personnel should maintain a nonhomophobic attitude, communicate clearly and sensitively using gender-neutral terms, and recognize how their own attitudes affect clinical judgments [293; 297]. Confidentiality is an important issue for MSM, and healthcare personnel should assure the patient that some information could be kept out of the medical record [240].

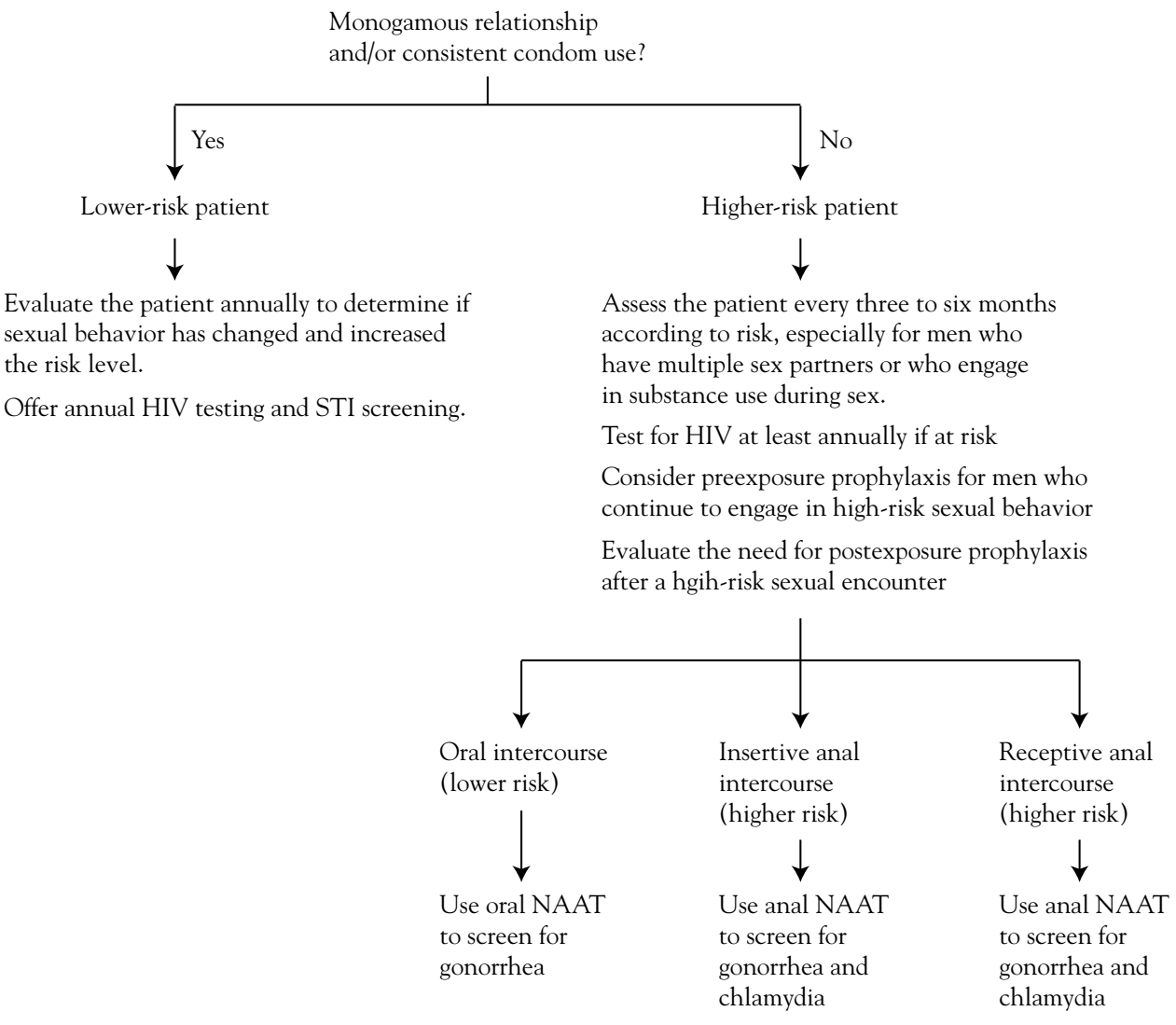
Comprehensive health care for MSM must focus on the population's disproportionate risks for several conditions, including STIs, anal and other types of cancer, substance misuse, eating disorders, suicide, and victimization [294]. Thus, it is essential for clinicians to address several issues with MSM [58; 173; 292; 298]:

- Use of safe sexual practices
- Screening and immunization for hepatitis A and B viruses
- Testing and consideration of pre-exposure prophylaxis for HIV infection
- Routine screening for STIs
- Routine screening for anal HPV-related neoplasia
- Potential risk for specific cancers (testicular, Hodgkin lymphoma, Kaposi sarcoma)
- Assessment of substance misuse (tobacco, alcohol, cocaine, methamphetamine)
- Nutrition and exercise
- Evaluation of psychologic well-being and mental health
- Screening for violence

Health risks should be addressed at the patient's first visit and each subsequent visit [58]. An algorithm has been developed to help guide recommended screening for MSM (***Figure 3***) [58]. In addition, because of an increased risk of HPV-related cancer, the ACIP now recommends HPV vaccination for MSM up to 26 years of age if they did not receive the vaccine when they were younger [276].

ALGORITHM FOR SCREENING MEN WHO HAVE SEX WITH MEN

Screen for previous immunizations for human papillomavirus and hepatitis A and B viruses.
Screen for hepatitis C virus if at risk.
Screen annually for behavioral disorders and substance use
Screen for STIs as outlined below.



NAAT = nucleic acid amplification testing.

Source: Reprinted with permission from Preventive health care for men who have sex with men. June 15, 2015, Vol. 91, No. 12, American Family Physician. Copyright © 2015 American Academy of Family Physicians. All rights reserved. *Figure 3*

EVIDENCE-BASED PRACTICE RECOMMENDATION

The CDC recommends clinicians should evaluate all adult and adolescent patients who are sexually active or who are injecting illicit drugs and offer to prescribe pre-exposure prophylaxis to persons whose sexual or injection behaviors and epidemiologic context place them at substantial risk of acquiring HIV infection.

(https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf. Last accessed June 6, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

Sensitivity should be used in obtaining the medical and sexual history, and the sexual history should be placed in context by emphasizing that an understanding of sexual behaviors is essential to evaluating risks and providing optimal care. It should also be noted that a sexual history is an important component in the care of all patients, regardless of their sexual orientation or behaviors. Because of the various stages a man may be in with respect to his sexual identity, care should be taken to distinguish sexual behavior from sexual identity [295; 297].

It is also vital to have resources readily available to provide to MSM as needed. Such resources include information on STI clinics, substance misuse facilities, services for victims of abuse, and referrals for counseling. The Gay and Lesbian Medical Association (GLMA) has developed resources to help clinicians provide appropriate care to gay, lesbian, bisexual, and transgender individuals. The GLMA also has a guideline for the care of this population, and the brochure (available at http://www.glma.org) includes a variety of additional resources [295].

HEALTH ISSUES FOR TRANSMEN

It is likely that most healthcare providers will encounter transgender individuals in the course of their professional careers, and all healthcare agencies and providers should be prepared to provide competent and compassionate care for gender-variant individuals. Based on data from 2008, the prevalence of female-to-male (FTM) transsexualism (transmen) is 1 in 30,400–200,000 [362]. A transman is a transgender individual who, assigned female at birth, currently identifies as a man. It is important to note that these patients are men and do not require additional description unless medically necessary.

Caring for transgender individuals is complex and requires some preparation and forethought, taking into account knowledge of anatomical reassignments, the effects of therapy, and cultural sensitivity. Very little has been published regarding the unique ongoing healthcare needs of patients who have undergone gender confirmation. In general, health care should be based on the treatments the patient has received and at what stage he may be in the gender transition. Health promotion awareness and health screening will vary somewhat, but generally the patient will have the same needs as most adult patients in a primary care setting; the patient's gender confirmation process will have little effect on many aspects of health care [363]. Basic preventive services, like sexually transmitted infection testing and cancer screening, can be provided without specific expertise in transgender care [364]. Keep in mind that in some cases, older transmen may not disclose their transgender history to their healthcare providers, as they initially sought treatment at a time when it was common for providers to use very strict guidelines to determine who could and could not receive treatment [365].

For the FTM patient, any residual female organs will require lifelong modified physical exams and risk screenings. These patients may require occasional modified pelvic exams and/or mammograms, and both the provider and the patient may have difficulty finding a comfortable clinical environment [366]. For FTM individuals, gynecologic examinations can heighten their emotional conflict between self-perception and physical anatomy. Respectful communication that maintains dignity, agency, and control is central to mitigating distress during pelvic exams [367]. The routine physical exam should include a breast exam, Pap test, and assessment of bone health and other possible effects of long-term testosterone supplementation.

PSYCHOSOCIAL WELL-BEING OF MEN

Psychosocial well-being is important to men, and many conditions or situations can disrupt the sense of well-being. Among the more common factors that can have a negative effect on well-being for both sexes are everyday stressors (positive as well as negative), personal conflicts, traumatic events, and depression. In general, men lack the social support and interpersonal relationships that help women to cope with stresses [299]. Because of this, men differ in their ability to handle stress, with many men resorting to anger, violence, and substance misuse to deal with stress or depression [28; 300]. As a result, stress/anger, substance misuse, and depression are among the psychosocial conditions with the most serious health implications for men. Most men will not seek help for psychosocial disorders and may not recognize the symptoms of depression [45; 300; 301]. Thus, it is important for healthcare providers to address psychosocial well-being and potential threats to well-being as part of routine health evaluations of men.

STRESS/ANGER

Stress and anger have long been associated with negative health consequences. Most of the earlier research focused on the effects of stress and hostility on coronary heart disease, and additional research has found a link between hostility and a more rapid decline in lung function in older men [302; 303; 304]. Appropriate expression of anger has been suggested as a way to improve health, and controlling anger has been shown to promote well-being in older individuals [305].

Safety is also of concern, as anger has been associated with an increased incidence of injuries and violence. In one study, higher levels of anger (at a given moment) were associated with an increased risk of injury, especially in men [306]. In that study, nearly 32% of individuals who had been injured reported having some degree of irritability before the injury. Men are the usual perpetrators of intimate partner violence causing injury, and these men tend to be younger (18 to 35 years of age), to be from a racial/ethnic minority population, and to have low socioeconomic status [307; 308]. Substance misuse and unemployment are also associated with such violence [307]. However, identifying a perpetrator of intimate partner violence in a clinical setting is difficult [308]. It is important to remember that men can also be victims of intimate partner violence, and this is especially true for MSM [309].

Although the USPSTF found insufficient evidence for or against routine screening for intimate partner violence (including child abuse and elder abuse), a survey of patients within a private family practice network showed that 97% of respondents believed that physicians should ask patients about family stress and conflict [310; 311]. The survey sample included women who had been physically hurt by intimate partner violence as well as men who had admitted perpetrating such injury. These findings support early studies that indicated patient preference for clinicians to ask questions about physical and sexual abuse [312]. The American Academy of Family Physicians (AAFP) notes that family physicians have the opportunity to provide early intervention in family violence through routine screening and identification of abuse; thus, physicians should be alert for the presence of family violence in virtually every patient encounter [313]. It seems reasonable and appropriate for clinicians to include within routine health assessments of men questions about feelings of anger and frustration and urges to strike family members [307; 309]. Suggestions for strategies that focus on anger management and conflict resolution may be helpful, especially for adolescents and young men [309].

SUBSTANCE MISUSE

As noted, substance misuse is higher among men than among women in all age categories, and men are more likely to have psychosocial problems related to the misuse [28; 307]. Although the rate of alcohol misuse is highest among younger men, men older than 65 years of age are of special concern because they are much more likely than women to be "problem" drinkers and to misuse a wide range of illicit as well as prescription drugs [307]. As the general population ages, the misuse of illicit drugs is expected to increase [314]. Adding to this problem is the low rate of screening for alcohol misuse in the older population and the secrecy of many men about drug use [314; 315].

Additional concerns are the use of anabolic steroids among adolescents and young adult men and the use of methamphetamine among MSM. Use of anabolic steroids begins during the teenage years in approximately 25% of cases, and about 10% of all users are teenagers [316]. The prevalence of methamphetamine use among MSM is approximately 10% to 20%, a rate that is 10 times higher than that in the general population [317].

Several professional organizations, including the USPSTF, recommend screening and behavioral counseling intervention to reduce alcohol misuse [318]. However, reported rates of screening have been low [319]. Several screening instruments have been developed, and they vary in the number of questions, the populations for which they are best suited, and their usefulness in specific situations; no one tool is perfect [320; 321; 322; 323]. The CAGE questionnaire, which includes four questions, is best for detecting alcohol dependency and is easy and quick to perform [320; 321]. However, the test may not detect low, but risky, levels of drinking [307; 324]. The Alcohol Use Disorders Identification Test (AUDIT) is the most accurate for detecting problem drinking [319; 322].

Screening in the older population is especially important, as low levels of alcohol use can cause morbidity due to age-related physiologic changes, comorbidities, and the use of prescription medications [325]. Screening tools developed specifically for older individuals should be used, such as the geriatric version of the Michigan Alcohol Screening Test (MAST) or the Alcohol-Related Problems Survey (ARPS) [325; 326; 327]. Clinicians should also ask specific questions about drug use.

A medical history is also helpful, and a family history of alcoholism is a risk factor [319]. Clues to a problem with alcohol can be provided by such symptoms as amnesic episodes, mood swings, chronic fatigue, gastrointestinal symptoms, anxiety, and excessive sweating [319]. Several physical findings can suggest that a patient has a problem with alcohol or drugs, including [319; 324]:

- Mild tremor
- Unsteady gait
- Tachycardia
- Odor of alcohol or marijuana
- Enlarged, tender liver
- Nasal irritation (cocaine use)

- Conjunctival irritation (marijuana use)
- Excessive use of aftershave or mouthwash
- Signs of chronic obstructive pulmonary disease, hepatitis B or C, or HIV infection

Signs that should raise a "red flag" about substance misuse are frequent absences from work or school, history of frequent trauma or accidental injuries, depression or anxiety, other substance misuse, labile hypertension, sexual dysfunction, sleep disorders, poor nutrition, gastrointestinal symptoms, and interpersonal conflicts [307; 319; 324].

Clinicians should provide brief interventions, such as short counseling strategies, for men who are identified to have at-risk drinking. These interventions have been shown to be effective [284; 319; 324]. Alcoholism and drug addiction are best treated by an addiction medicine specialist or through an inpatient or outpatient program [324]. Primary care providers should have referrals for counseling and treatment readily available, as well as resources on support groups, such as Alcoholics Anonymous and Narcotics Anonymous.

To help healthcare professionals carry out the appropriate diagnosis and treatment of patients with alcohol problems, the National Institutes on Alcoholism and Alcohol Abuse (NIAAA) developed the publication *Helping Patients Who Drink Too Much: A Clinician's Guide*, which features an updated guideline on screening and brief intervention. The most recent edition is available on the NIAAA website at https://pubs.niaaa.nih.gov/publications/practitioner/cliniciansguide2005/guide.pdf.

DEPRESSION

Depression is often regarded as a "woman's disease" because it is diagnosed more frequently in women than men. However, researchers and the health community at large now realize that depression is of serious concern in men and is underdiagnosed [28; 328]. According to data from 2020, the prevalence of major depressive episode was 6.2% among men and 10.5% among women [329].

Despite the lower rates of depression in men compared with women, the rate of completed suicide is nearly four times higher for men (25.8 vs. 7.1 per 100,000) [25]. Suicide is a leading cause of death for men in many age groups and across all racial/ethnic populations, except for the Black population [25].

The underdiagnosis of depression in men involves clinician-related and patient-related factors. Clinicians' lack of appropriate training and discomfort with dealing with depression contribute to a low rate of diagnosis, estimated to be about 50% [3; 330]. In addition, no screening instrument for suicide risk has been shown to reliably detect suicide risk in primary care populations [331]. This is unfortunate, as primary care providers appear to be in a position to intervene. As many as 83% of people who died by suicide had contact with their primary care physician in the year before death, with approximately 20% seeing their physician one day before death [330; 332]. In addition, 50% to 66% of individuals who committed suicide saw their primary care physician within one month of their death, with 10% to 40% committing suicide within one week of the visit [331]. Thus, better recognition of depression and suicide risk by primary care providers may help reduce suicide rates.

Many patient-related factors in the underdiagnosis of depression are primarily related to gender issues, including [28; 300; 328; 330; 333; 334]:

- Reluctance of men to seek help
- Lack of men's recognition of the symptoms of depression
- Hesitancy of men to express emotions
- Tendency for men to see depression as a weakness
- Men's misconceptions about mental illness and its treatment

Diagnosis

Because men are less likely to express their emotions, they may recognize and discuss only the physical symptoms of depression, making diagnosis a challenge [300; 301; 333]. A carefully taken history can elicit information about risk factors, which include a family history of depression, the use of some medications (beta blockers, histamine H2-receptor antagonists, benzodiazepines, and methyldopa), chronic illness or other comorbidity, lack of social support, recent life stressor, and single marital status [307; 335]. Substance misuse frequently occurs concomitantly with depression, more often in men than women, but the direction of the causal relationship is not clear [300; 335].

Many of the symptoms of depression reported by women are the same for men: depressed mood, changes in appetite and sleep habits, problems with concentration, and an inability to find pleasure in once pleasurable activities [300]. It has been proposed that the symptoms of depression in men represent a male depressive syndrome, characterized by such symptoms as irritability, acting-out, aggression, low tolerance of stress, low impulse control, tendency to blame others, and a greater willingness to take risk [28; 300; 330; 333]. Men with depression may thus present with a very different symptom profile [328].

Identification of suicide risk is an essential component of the evaluation of patients with depression. Many of the risk factors for suicide are similar to those for depression; when the circumstances surrounding completed suicides were reviewed, the following were found to be factors [25]:

- Loss of a partner (through death or other means)
- Loss of job
- History of mental illness
- Depressed mood
- Previous suicide attempts
- Physical health problems
- Intimate partner problem
- Preceding or impending crisis (within two weeks)
- Financial problem

Clinicians should ask questions to determine the duration of symptoms and explore possible triggers of depression [328]. Because of their lack of experience with discussing emotions, many men may be uncomfortable with open-ended questions such as, "How do you feel?"; rather, discussing emotions in situational contexts can help men better express what they are feeling and why [333]. It may also be helpful to de-emphasize the negative connotation of depression and frame questions within the overall context of health and well-being [314].

Treatment Options

The treatment approach will depend on the severity of symptoms and the patient's preference. In general, a combination of psychotherapy and pharmacologic management provides the best results for most men [328; 335]. Potential psychotherapy approaches include cognitive behavior therapy and interpersonal psychotherapy [300; 307; 328]. First-line pharmacologic treatment involves the use of selective serotonin reuptake inhibitors, such as paroxetine, sertraline, and fluoxetine [307]. This treatment approach has efficacy rates of 30% to 70% [328]. Clinicians should emphasize the importance of taking the medication as prescribed, as it may be two to four weeks before a benefit is evident [328]. Depression that is associated with chronic illness is often seen as an inevitable consequence of the disease, but the depression should be treated. Frequently, the treatment improves the overall outcome [335].

FOSTERING ENHANCED HEALTH BEHAVIORS IN MEN

The strong association between lifestyle choices and men's morbidity and mortality clearly demonstrates the need to foster healthier behaviors among men. Creating a better understanding of the importance of health care requires broad-scale campaigns to heighten awareness of the need for routine and preventive health care and to encourage men to schedule physician visits. Also needed are efforts at the community and practice levels to enhance health-seeking behavior and improve men's understanding of their health. The efficacy of all of these efforts depends on addressing the unique features of the masculine gender identity.

LARGE-SCALE CAMPAIGNS

The Men's Health Network has established International Men's Health Week as the week leading up to Father's Day each June [336]. Highlights of the Week include health fairs, screening, and distribution of educational materials in workplaces and elsewhere in the community. Other Men's Health Network campaigns "speak" to men, with names such as "Men at Work" and "Time Out for Men's Health" maintenance schedule [336].

Some have suggested that large-scale campaigns that feature well-respected athletes and actors can increase appeal to men [45]. However, others have cautioned that, while celebrity endorsement of screening may have a positive effect on men, such campaigns may not target the right audience or address all the pertinent facts [337].

The optimal educational campaigns are those that target men and attempt to challenge men's perceptions of health and the need for preventive care. For example, to heighten awareness about depression in men, the National Institute of Mental Health launched the "Real Men, Real Depression" campaign and produced an accompanying booklet "Men and Depression" [335]. Both the campaign and the booklet feature quotations and vignettes from men who have been treated for depression.

Analysis of data about men who lack a usual source of care indicates that such men are more apt to be younger, Hispanic, single (never married or divorced), without insurance, and living in the southern or western parts of the United States or in urban areas [39]. Education about the importance of health care should be provided through public service announcements, media, schools, and workplaces as appropriate to target these groups of men [39]. Given men's propensity to see a physician only when they are sick or have symptoms, educational messages should emphasize the importance of preventive visits and discourage symptoms as a motivator for seeking health care [338]. Resources should also be culturally appropriate for diseases and conditions that disproportionately affect men of certain races and ethnicities.

As a result of men's reluctance to seek help, educational strategies that provide anonymity may be particularly well-suited for them [45; 339]. Print resources should be distributed through a variety of venues that men frequent, such as the workplace, schools, religious organizations, sports arenas, men's organizations or clubs, pubs, supermarkets, car and motorbike dealerships, and barbershops [45; 339; 340]. In addition, digital media may be effective, especially for younger men. A study showed that 90-second educational video clips on men's health, sent by e-mail, were well-received [341].

Many community-based educational programs targeting men have been successful, especially among men in racial/ethnic minority populations. For example, a culturally tailored, language-concordant navigator program was successful at improving rates of colorectal cancer screening at a healthcare center serving a low-income, ethnically and linguistically diverse community [342]. The Black Barbershop Health Outreach Program (BBHOP) has been an effective program for promoting cardiovascular health, and the program can be used as a model for other health topics [343]. Another barbershop-based program involves training barbers to educate their clients about prostate cancer [344]. Focus groups of men from churches of a variety of denominations have indicated that church-based education may also be effective [35; 345].

PRACTICE-LEVEL STRATEGIES

Men are more likely to use healthcare services that are quick and easy; consequently, making physician visits more convenient may increase the number of men who seek health care [339; 346]. Evening office hours and walk-in appointments may be helpful in addressing this problem, and male-specific group appointments have been effective in enhancing men's education on health issues, with high satisfaction reported by participants [347]. In addition, nontraditional settings for healthcare services have been suggested, such as within workplaces and near sports venues, shopping centers, and men's organizations [45; 339].

Men who are most likely to seek preventive care are those who live with a spouse or partner [348]. In addition, men have been shown to have strong feelings about women as the arbiters of health for the entire family and are likely to be influenced to seek health care by a member of the opposite sex; this is especially true for men in racial/ethnic minority populations [35; 40; 43; 45]. Given these findings, healthcare providers should talk to their female patients to emphasize the importance of encouraging the men in their families to seek routine health care. Additionally, all interactions with male patients should be used to promote routine health assessments. Men who seek help for acute problems should be reminded of the need for screening and be counseled about risk factors [45; 349]. A subsequent visit should be encouraged, and this message may be reinforced by providing a take-home reminder or by scheduling an appointment while the patient is in the office [45].

As noted earlier, fostering open communication in a nonjudgmental manner is essential. Clinicians should take care to raise health issues with their male patients and to overcome some masculine traits in communication, such as a reluctance to ask questions [240]. Asking open-ended questions may be helpful in some cases, and providing a questionnaire before the visit may foster discussion [45]. Assumptions about a man's willingness to share information should be avoided, as men have been more forthcoming when they receive cues that they are expected to provide valuable information [350]. Lastly, men often have a need to feel empowered, and shared decision making is important [351].

Decision aids are available in a variety of formats and literacy levels, and they may be useful in helping men make informed decisions about care [119; 129; 130; 131]. Also, clinicians should review decision aids and educational resources carefully before using them to ensure that the information is comprehensive and accurate [129]. Resources should be available about the risks involved with not wearing a safety belt or motorcycle helmet, driving while intoxicated, speeding, handling firearms, stress/anger management, and safety issues in the home and at work.

Clinicians can help ensure that their patients receive reliable online information by posting the addresses of authoritative websites in their office, in print resources, and within the community (***Table 18***). Healthcare providers should be familiar with established guidelines for screening among men in various age categories and should emphasize the relative benefits and disadvantages of screening (***Table 19***). The Electronic Preventive Services Selector (ePSS) is an application for mobile devices that provides USPSTF information on screening and counseling, as well as preventive medication services. The AUA offers the Men's Health Checklist, a compact, downloadable reference for coordinating care of men; it is available at https://www.auanet.org/publications/mens-health-checklist.

Routine health assessments should include screening and counseling about lifestyle factors that have an impact on health, such as substance misuse, diet, exercise, safe sex practices, and sun protection. Education about sun protection and self-examination for moles is especially important given the increase in the lifetime risk for melanoma among men [24]. At each routine visit, healthcare providers should assess each male patient's individual lifestyle, psychosocial, and occupational risks. The high rate of unintentional injury as a cause of death for men calls for increased attention to safety issues.

ONLINE HEALTH RESOURCES FOR MEN
General
American Heart Association *Information on cardiovascular disease, diabetes, cerebrovascular disease; tools for healthy lifestyle habits (diet, exercise, smoking) ("Getting Healthy" section).* https://www.heart.org
Centers for Disease Control and Prevention Men's Health *Area devoted to men's health issues.* https://www.cdc.gov/nchs/fastats/mens-health.htm
Men's Health Network *Site devoted to men's health issues. Publishes Blueprint for Men's Health: A Guide to a Healthy Lifestyle.* https://www.menshealthnetwork.org
Cancer
American Cancer Society *Cancer prevention and early detection worksheet for men—a tool to help men identify risks and understand preventive measures and early detection strategies for prostate cancer and lung cancer; includes links to information on various types of cancer. Information on prevention, screening, diagnosis, and treatment of all types of cancer.* https://www.cancer.org
National Cancer Institute *Information on prevention, screening, diagnosis, and treatment of all types of cancer.* https://www.cancer.gov
National Comprehensive Cancer Network *Patient guides (based on evidence-based guidelines) on the treatment of a variety of cancers.* https://www.nccn.org/patientresources/patient-resources
Smoking Cessation
Centers for Disease Control and Prevention Smoking and Tobacco Use https://www.cdc.gov/tobacco
National Cancer Institute https://www.cancer.gov/about-cancer/causes-prevention/risk/tobacco
Genitourinary Disorders
Urology Care Foundation, The Official Foundation of the American Urological Association *Information on benign prostatic hypertrophy, prostate cancer, erectile dysfunction, and other urologic conditions.* https://www.urologyhealth.org
Depression
National Institute of Mental Health *Articles on depression in men, as well as personal stories of men with depression.* https://www.nimh.nih.gov/health/topics/depression
Alcohol and Drug Use
National Institute on Alcohol Abuse and Alcoholism *Research-based information on drinking its effect on health.* https://www.niaaa.nih.gov/alcohol-health
National Institute on Drug Abuse https://nida.nih.gov
Sexually Transmitted Infections
Centers for Disease Control and Prevention Sexually Transmitted Diseases https://www.cdc.gov/std
Source: Compiled by Author — *Table 18*

RECOMMENDATIONS AND SUGGESTIONS FOR HEALTH ASSESSMENTS, SCREENING, AND COUNSELING FOR MEN			
Intervention	**Suggested Frequency**	**Relevant Ages (Years)**	**Recommending Body/Source**
Routine physical examination (with determination of height, weight, and body mass index)	Every 3 to 5 years	18 to 39	—
	Every 1 to 2 years	40 to 49	
	Yearly	50 and older	
Blood pressure screening	Every 1 to 2 years, depending on blood pressure	Beginning at 18	USPSTF
Cholesterol level/lipid profile	At least every 5 years	40 to 75 (earlier if at increased risk)	USPSTF
Diabetes (type 2) and prediabetes screening	Every 3 years	35 to 70 in men with overweight or obesity	USPSTF
Cancer-related check-up (for cancer of the thyroid, testicles, lymph nodes, oral cavity, and skin)	At each routine examination	Beginning at 20	ACS
Assessment, Counseling, and Behavioral Interventions as Appropriate			
Tobacco use	At each routine examination	All men	USPSTF
Alcohol use	At each routine examination	All men	USPSTF
Drug (illicit) use	At each routine examination	All men	ASAM
Depression	At each routine examination, when staff-assisted depression care supports are in place	All men	USPSTF
Counseling			
Healthy diet	At each routine examination	Men with risk factors for cardiovascular disease and diet-related chronic diseases	USPSTF
Exercise	At each routine examination	All men	AAFP, AMA, AHA, CDC
Sun avoidance and use of sunscreen	At each routine examination	All men	ACS, AAD, NIH Consensus Panel
Skin examination for melanoma	At each routine examination	All men	ACS
Avoidance of sexually transmitted infections	At each routine examination	All sexually active men at increased risk	CDC
Risk of HIV infection	At each routine examination	All men who have sex with men	AAFP
Risk for hepatitis A and B	At each routine examination	All men who have sex with men and others at high risk	AAFP
Sexual health	At each routine examination	All men	AAFP

Table 19 continues on next page.

RECOMMENDATIONS AND SUGGESTIONS FOR HEALTH ASSESSMENTS, SCREENING, AND COUNSELING FOR MEN *(Continued)*			
Intervention	**Suggested Frequency**	**Relevant Ages (Years)**	**Recommending Body/Source**
Screening			
Colorectal cancer	Every 1 to 10 years, depending on risk and test used	45 to 75	USPSTF
Osteoporosis	At each routine examination	By 65	ACP
HIV	Not established (encourage men to be tested)	15 to 65 (younger and older men at increased risk)	USPSTF
Visual acuity (comprehensive eye examination)	Yearly	Beginning at 65	AAO
Abdominal aortic aneurysm (ultrasonography)	Once	65 to 75 (men who have ever smoked)	USPSTF
Immunizations			
Tetanus, diphtheria, pertussis (Td/Tdap)	Once (Tdap), with booster (Td or Tdap) every 10 years	All men	ACIP
Influenza vaccine	Yearly	All men	ACIP
Pneumococcal vaccine	Once	65 and older (19 to 64 if risk) (one or two doses, depending on vaccine)	ACIP
Hepatitis A	Once	All men, if risk factors are present (2 or 3 doses, depending on vaccine)	ACIP
Hepatitis B	Once	19 to 59, and 60 and older if risk factors are present (2, 3, or 4 doses, depending on vaccine or condition)	ACIP
Human papillomavirus (HPV)	Once	19 to 26 (2 or 3 doses depending on age at initial vaccination and condition) 26 to 45, if desired based on shared clinical decision making	ACIP
Zoster (shingles)	Once	50 and older or younger if risk factors present (2 doses)	ACIP
Haemophilus influenzae type b (Hib)	Once	All men, if risk factors present (1 or 3 doses depending on indication)	ACIP
Meningococcal A, C, W, Y	Once	All men, if risk factors present (1 or 2 doses depending on indication)	ACIP
Meningococcal B	Once	All men, if risk factors present (2 or 3 doses depending on vaccine and indication)	ACIP
Source: [58; 284; 298; 352]			*Table 19*

CONCLUSION

In response to high morbidity and mortality rates among men over the past decade, researchers have focused increased attention on men's health issues. Many factors contribute to health-related gender disparities, but male gender identity is thought to have the most significant impact. The characteristics of the traditional male role (self-reliance, independence, and maintenance of a strong image) cause men to seek health care much less often than women, especially for preventive care. As a result, disease in men may remain undiagnosed until more advanced stages. A tendency for risky behavior, another aspect of the traditional male role, also has a significant effect on men's mortality, as evidenced by unintentional injury being the third leading cause of death among all men. Such behaviors as substance misuse and non-use of protective devices (safety belts, helmets) begin in adolescence and continue into adulthood; across all age-groups, the rates of these behaviors are higher for male individuals than for female individuals. These behaviors are strongly associated with both chronic diseases and all-cause mortality in men.

Prostate cancer is a major concern for many men, and the issues of prostate cancer screening and treatment options are complex and confusing for patients as well as healthcare professionals. Informed decision making is also an important aspect of many benign conditions, such as prostatitis, BPH, premature ejaculation, erectile dysfunction, and late-onset hypogonadism. These conditions have a substantial effect on the quality of life for men, yet men are reluctant to initiate conversations on these topics because of embarrassment and a hesitancy to express feelings and symptoms. It is important to create an environment of open dialogue and ask questions to help men discuss these topics.

The psychosocial well-being of men is important for overall health. Alcohol misuse and depression have both been underdiagnosed in men, especially older men, and clinicians should remain diligent in screening for these disorders in their male patients.

Improvement of men's health relies on men gaining a greater understanding of their risk factors and becoming more involved in the health issues that affect them. Healthcare professionals have a critical role in helping to develop strategies to enhance men's utilization of healthcare resources and in encouraging their male patients to engage in screening and preventive care and to adopt healthy behaviors. Health assessments and screening should be carried out according to established guidelines, with consideration given to each individual patient's specific risks.

Customer Information/Answer Sheet/Evaluation insert located between pages 96–97.

COURSE TEST - #93764 MEN'S HEALTH ISSUES

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

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

This 15 credit activity must be completed by June 30, 2025.

1. Which of the following causes of death occurs at a higher rate for men compared with women?
A) *Stroke*
B) *Suicide*
C) *Alzheimer disease*
D) *Pneumonia/influenza*

2. Which of the following statements about deaths caused by unintentional injury is TRUE?
A) *The highest rate is found among White men.*
B) *The number of occupational deaths is higher for men than women.*
C) *The number of deaths related to motor vehicle accidents is lower for men than women.*
D) *The number of deaths caused by unintentional injury among men in the United States is lower than the median for every other country around the world.*

3. Which of the following best describes the effect of male gender identity on men's health?
A) *Men are more likely than women to have screening tests.*
B) *Most men seek care as soon as possible when they are sick.*
C) *Men are more likely than women to lack a usual source of health care.*
D) *Men are forthcoming about symptoms with their healthcare providers.*

4. When diagnosing prostatitis,
A) *the evaluation should not include a urinalysis and urine culture.*
B) *the Meares-Stamey test is helpful for diagnosing chronic pelvic pain syndrome.*
C) *a history of recurrent urinary tract infections is indicative of acute bacterial prostatitis.*
D) *the National Institute of Health (NIH) Chronic Prostatitis Symptom Index should be completed to obtain a baseline for the severity of symptoms.*

5. Which of the following statements about the treatment of chronic prostatitis/chronic pelvic pain syndrome is most accurate?
A) *Trimethoprim should not be used.*
B) *Pregabalin has improved symptoms.*
C) *An alpha-blocker alone has provided more benefit than an alpha-blocker plus antibiotic.*
D) *Fluoroquinolones have improved symptoms even when no bacterial cause has been identified.*

6. An established risk factor for benign prostatic hypertrophy (BPH) is
A) *Asian race.*
B) *increased age.*
C) *a genetic mutation*
D) *family history of cancer.*

7. In regard to the prevention of prostate cancer, finasteride has been associated with
A) *increased time to onset of disease.*
B) *decreased risk for all-cause mortality.*
C) *increased risk for high-grade prostate cancer.*
D) *increased risk for prostate cancer-specific mortality.*

8. Prostate cancer screening has been shown to lead to
A) *lower mortality rates.*
B) *decreased need for biopsy.*
C) *diagnosis at an earlier stage.*
D) *higher prevalence of definitive disease.*

Test questions continue on next page ➔

9. A man has clinically localized prostate cancer (T1c), with a Gleason score of 4 and a PSA level of 8 ng/mL. He is 68 years of age and has a life expectancy of more than 10 years. According to NCCN guidelines, which of the following is the recommended approach?
A) *Radiation therapy*
B) *Active surveillance*
C) *Radical prostatectomy*
D) *Androgen deprivation therapy*

10. The recommended initial therapy for metastatic prostate cancer is
A) *brachytherapy.*
B) *chemotherapy.*
C) *radical prostatectomy.*
D) *androgen deprivation therapy.*

11. The primary symptom associated with acute epididymitis is
A) *urinary retention.*
B) *unilateral tenderness.*
C) *pain with extended standing.*
D) *sudden onset of pain in both testicles.*

12. Varicoceles usually are
A) *more common in infertile men.*
B) *a source of substantial unilateral pain.*
C) *more pronounced when the patient is recumbent.*
D) *associated with a hardness of the testes in older men.*

13. Nonseminoma testicular cancer is associated with an elevated
A) *AFP level.*
B) *LDH level.*
C) *beta-hCG level.*
D) *beta-hCG level and a normal AFP level.*

14. The primary adverse effect of chemotherapy for testicular cancer is
A) *hearing loss.*
B) *oligospermia.*
C) *erectile dysfunction.*
D) *secondary leukemias.*

15. Which of the following statements about male breast cancer is most accurate?
A) *Lumpectomy is rarely performed.*
B) *The BRCA2 mutation is found in most cases.*
C) *Adjuvant hormone therapy has a limited role in treatment.*
D) *Sentinel lymph node biopsy has not been found to be effective.*

16. Which of the following has the strongest association with erectile dysfunction?
A) *Obesity*
B) *Depression*
C) *History of smoking*
D) *Cardiovascular disease*

17. All four phophodiesterase-5 inhibitors used for treatment of erectile dysfunction are similar with respect to
A) *serum half-life.*
B) *side effect profile.*
C) *duration of action.*
D) *time to maximum serum level.*

18. Late-onset hypogonadism is
A) *equivalent to menopause in women.*
B) *well defined by a level of testosterone.*
C) *similar to hypogonadism in younger male individuals.*
D) *associated with a loss of sexual satisfaction and overall well-being.*

19. Male infertility
A) *is correctable in most cases.*
B) *is not affected by prescription medications.*
C) *is the only cause in most cases of infertile couples.*
D) *affects men younger than 25 years of age twice as often as older men.*

20. According to the CDC, men who are evaluated for gonorrhea should also be evaluated for infection with
A) *chlamydia.*
B) *hepatitis B.*
C) *herpes simplex virus 2.*
D) *human papillomavirus.*

21. Which of the following is recommended by the CDC for the treatment of gonorrhea?

A) Acyclovir
B) Benzathine penicillin
C) Ceftriaxone and doxycycline
D) Azithromycin and penicillin G

22. According to Figure 3, which of the following statements about screening for men who have sex with men is TRUE?

A) High-risk patients should be assessed yearly.
B) Annual HIV screening should not be considered for low-risk men.
C) Hepatitis A and B immunization should be assessed in high-risk patients only.
D) Anal NAAT should be considered for men who have receptive anal intercourse.

23. Which of the following statements about substance misuse is TRUE?

A) The misuse of illicit drugs is expected to decrease as the general population ages.
B) The rate of alcohol misuse is higher among younger women than among younger men.
C) Men are less likely than women to have psychosocial problems related to substance misuse.
D) Men older than 65 years are much more likely to be "problem" drinkers than women in that age group.

24. The depression treatment approach that offers the best results for most men is

A) pharmacologic therapy alone.
B) cognitive behavioral therapy alone.
C) interpersonal psychotherapy alone.
D) psychotherapy and pharmacologic therapy.

25. A study has shown that which of the following may be effective for educating younger men about health issues?

A) Health fairs
B) Support groups
C) Short video clips
D) Pamphlets emphasizing the importance of prevention

Be sure to transfer your answers to the Answer Sheet insert located between pages 96–97.
PLEASE NOTE: Your postmark or facsimile date will be used as your test completion date.

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MODERATE SEDATION

#40953 • 5 Credits

Book By Mail – $33 • **ONLINE – $25**

Mandate: VA

Purpose: The purpose of the course is to provide physicians with the information necessary to perform moderate sedation safely and according to existing guidelines in order to facilitate better patient care.

Audience: This course is designed for physicians in a variety of settings, including private practice, emergency department, radiology department, cardiac catheterization lab, and ambulatory surgery centers. The course is also of benefit to private practice physicians in family medicine and virtually all specialty areas.

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

Special Approvals: This course meets the Virginia requirement for 4 hours of anesthesia education.

RISK MANAGEMENT

#41473 • 5 Credits

Book By Mail – $33 • **ONLINE – $25**

Mandate: CT, MA, MI, NV, PA, RI, TX

Purpose: With patient safety as the priority, risk management should focus on the avoidance of medical errors, as they are, along with inadequate informed consent, the most common assertions in malpractice claims in the United States. The purpose of this course is to provide healthcare professionals with the information necessary to engage in risk management practices, including a variety of proven strategies to avoid malpractice.

Audience: This course is designed for physicians, physician assistants, and nurse practitioners seeking to enhance their knowledge of risk management strategies, especially in the outpatient setting.

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

Special Approvals: This course meets the Michigan, Nevada, and Texas requirements for ethics/professional responsibility education and meets the Connecticut, Massachusetts, Pennsylvania, and Rhode Island requirements for risk management education.

SAFE CLINICAL USE OF FLUOROSCOPY

#90471 • 10 Credits

By Mail – $58 • **ONLINE – $50**

Mandate: CA, MA (PAs)

Purpose: The purpose of this course is to provide healthcare providers with an understanding of the challenges encountered when using fluoroscopy in clinical practice and the tenets of safe fluoroscopy use in clinical practice.

Audience: This course is designed for physicians, nurses, radiology technicians, surgical technicians, and all healthcare staff involved in ensuring safe clinical use of fluoroscopy.

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

Special Approvals: This course meets the California requirement for 4 hours of education in radiation safety for the clinical uses of fluoroscopy and 10 hours of education on the application of x-ray to the human body. This course meets the Massachusetts physician assistant requirement for 4 hours of fluoroscopic imaging education.

COLORECTAL CANCER

#90782 • 15 Credits

Book By Mail – $83 • **ONLINE – $75**

Mandate: CA

Purpose: The purpose of this course is to provide healthcare professionals with information regarding the screening, diagnosis, and treatment of colorectal cancer in order to improve adherence to established guidelines and, by extension, patient outcomes.

Audience: This course is designed for physicians, physician assistants, nurses, and other healthcare providers who may improve the identification and care of patients with colorectal cancer.

Additional Approvals: ABIM, ABS, ABPath

Special Approvals: This course meets the California requirement for geriatric education.

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

#91602 • 3 Credits

Book By Mail – $23 • **ONLINE – $15**

Mandate: WV

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

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

Additional Approvals: ABIM, ABS, ABA, ABO

Special Approvals: This course fulfills the West Virginia Board of Examiners for Registered Professional Nurses requirement for 3 hours of education related to Drug Diversion and Best Practice Prescribing of Controlled Substances.

This course fulfills the West Virginia State Board of Examiners for Licensed Professional Nurses requirement for 3 hours of education related to Chemical Dependency/Substance Abuse.

This program has been approved by the WV Board of Medicine and will satisfy the required 3 hours of CME for Drug Diversion Training and Best Practice Prescribing of Controlled Substances Training for MDs and their licensed Physician Assistants.

Selected Course Availability List *(Cont'd)*

WHAT HEALTHCARE PROFESSIONALS SHOULD KNOW ABOUT EXERCISE

#91724 • 5 Credits

Book By Mail – $33 • **ONLINE – $25**

Purpose: The purpose of this course is to supply the information necessary for physicians and other healthcare professionals to provide practical advice for patients beginning an exercise program.

Audience: This course is designed for physicians and will be of interest to nurses and other healthcare professionals working with adult patients who are overweight or obese and should begin an exercise program.

Additional Approvals: ABIM, ABS, ABP

CHILD, ADOLESCENT, AND ADULT IMMUNIZATION SCHEDULES

#91743 • 5 Credits

Book By Mail – $33 • **ONLINE – $25**

Purpose: The purpose of this course is to provide healthcare professionals with the information necessary to identify patients who should be vaccinated and methods to increase vaccination coverage in outpatient practice.

Audience: This course is designed for healthcare professionals working in all practice settings who may encourage patients to receive appropriate vaccinations and improve the overall vaccination rates.

Additional Approvals: ABIM, ABS, ABP

PRESCRIPTION OPIOIDS AND PAIN MANAGEMENT: THE TENNESSEE GUIDELINES

#95131 • 2 Credits

By Mail – $23 • **ONLINE – $15**

Mandate: TN

Purpose: The purpose of this course is to provide clinicians who prescribe or distribute opioids with clinical guidance for management of chronic pain and opioid prescription drug use that conforms with Tennessee Department of Health guidelines and with clinical tools designed to assess the risk of drug-seeking and diverting behaviors. The goal is to promote best practice patient care and prevent the growing public health problem of drug misuse, diversion, and overdose.

Audience: This course is designed for all clinicians who may alter prescribing practices or intervene to prevent drug diversion and inappropriate opioid use.

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

Special Approvals: This course is designed to meet the Tennessee requirement for 2 hours of education on the prescribing of controlled substances, including instruction in the Tennessee Chronic Pain Guidelines.

ALZHEIMER DISEASE

#96153 • 15 Credits

Book By Mail – $83 • **ONLINE – $75**

Mandate: IL, MA

Purpose: In order to increase and maintain a reasonable quality of life for patients with Alzheimer disease throughout the course of the disease, caregivers must have a thorough knowledge and understanding of the disease. The purpose of this course is to provide clinicians with the skills to care for patients with Alzheimer disease in any setting as part of the interdisciplinary team.

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, ABO

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

HUMAN TRAFFICKING AND EXPLOITATION

#96313 • 5 Credits

By Mail – $33 • **ONLINE – $25**

Mandate: MI

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

Audience: This course is designed for physicians and other members of the interdisciplinary team who may intervene in suspected cases of human trafficking and/or exploitation.

Additional Approvals: ABIM, ABS, ABP, ABO

Special Approvals: This course meets the Michigan requirement for training in identifying victims of human trafficking.

SUICIDE ASSESSMENT AND PREVENTION

#96441 • 6 Credits

By Mail – $38 • **ONLINE – $30**

Mandate: CT, NV, TX, WA

Purpose: The purpose of this course is to provide health and mental health professionals with an appreciation of the impact of depression and suicide on patient health as well as the skills necessary to identify and intervene for patients at risk for suicide.

Audience: This course is designed for healthcare professionals who may identify persons at risk for suicide and intervene to prevent or manage suicidality.

Additional Approvals: ABIM, ABS, ABP, ABO

Special Approvals: This course meets the Connecticut requirement for 2 hours of behavioral health education. This course is approved by the Nevada State Board of Medical Examiners to fulfill 2 hours of Suicide Prevention and Awareness education. This course meets the Texas requirement for medical ethics/professional responsibility education. This course is approved by the State of Washington Department of Health to fulfill the requirement for Suicide Prevention training for healthcare professionals. Approval number TRNG.TG.60715375-SUIC.

ANXIETY DISORDERS IN OLDER ADULTS

#96690 • 3 Credits

Book By Mail – $23 • **ONLINE – $15**

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

Selected Course Availability List *(Cont'd)*

PSYCHEDELIC MEDICINE AND INTERVENTIONAL PSYCHIATRY

NEW!

#96790 • 10 Credits

Book By Mail – $58 • **ONLINE – $50**

Purpose: 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.
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.
Additional Approvals: ABIM, ABS, ABP

CANNABIS AND CANNABIS USE DISORDERS

#96973 • 5 Credits

Book By Mail – $33 • **ONLINE – $25**

Mandate: AK, AZ, CA, CT, MI, NM, NV, VA

Purpose: The purpose of this course is to allow healthcare professionals to effectively identify, diagnose, treat, and provide appropriate referrals for patients with cannabis use disorders.
Audience: This course is designed for health and mental health professionals who are involved in the evaluation or treatment of persons who use cannabis, either illicitly or as an adjunct to medical treatment.
Additional Approvals: ABIM, ABS, ABP, ABO
Special Approvals: This course meets the New Mexico requirement for 2 hours of cannabis education and the Oregon requirement for 3 hours of medical marijuana education. This course meets 5 hours of addiction education.

IMPLICIT BIAS IN HEALTH CARE

#97000 • 3 Credits

Book By Mail – $23 • **ONLINE – $15**

Mandate: CA, IL, MA, MI

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, ABO
Special Approvals: This course meets the California, Illinois, Massachusetts, and Michigan requirement for implicit bias training.

SEXUAL ASSAULT

#97022 • 3 Credits

By Mail – $23 • **ONLINE – $15**

Mandate: CT, SC, TX

Purpose: The purpose of this course is to address knowledge gaps, enhance clinical examination and management skills, and improve treatment outcomes for victims of sexual assault.
Audience: This course is intended for physicians and other healthcare professionals who may be called upon to provide care to victims of sexual assault.
Additional Approvals: ABIM, ABS, ABP, ABPath, ABO
Special Approvals: This course meets the Connecticut requirement for sexual assault education, the South Carolina requirement for encouraged education in domestic violence, and the Texas requirement for forensic evidence education for those who perform examinations on sexual assault survivors.

SEXUAL HARASSMENT PREVENTION: THE ILLINOIS REQUIREMENT

#97081 • 1 Credit

By Mail – $23 • **ONLINE – $15**

Mandate: IL

Purpose: The purpose of this course is to provide health and mental health professionals with clear knowledge of the consequences of sexual harassment and the skills to help combat harassment in the workplace.
Audience: This course is designed for members of the interprofessional healthcare team who may act to prevent sexual harassment.
Additional Approvals: ABIM, ABS, ABA, ABP, ABO
Special Approvals: This course is designed to fulfill the Illinois requirement for sexual harassment education.

PALLIATIVE CARE AND PAIN MANAGEMENT AT THE END OF LIFE

#97383 • 15 Credits

Book By Mail – $83 • **ONLINE – $75**

Mandate: CA, IA, MA, NJ, OR, RI, VT

Purpose: The purpose of this course is to bridge the gap in knowledge of palliative care by providing an overview of the concept of palliative care and a discussion of the benefits and barriers to optimum palliative care at the end of life.
Audience: This course is designed for all members of the interdisciplinary team, including physicians, physician assistants, nurse practitioners, nurses, social workers, marriage and family therapists, and other members seeking to enhance their knowledge of palliative care.
Additional Approvals: ABIM, ABS, ABA
Special Approvals: This course fulfills 11 hours of education on the appropriate care of the terminally ill for California-licensed physicians who must complete 12 hours of pain management and the appropriate care of the terminally ill. This course meets the Iowa, Massachusetts, New Jersey, Oregon, Rhode Island, and Vermont requirements for end-of-life education.

HUMAN TRAFFICKING AND EXPLOITATION: THE TEXAS REQUIREMENT

#97470 • 5 Credits

By Mail – $33 • **ONLINE – $25**

Mandate: TX

Purpose: The purpose of this course is to increase the level of awareness and knowledge about human trafficking and exploitation so health and mental health professionals can identify and intervene in cases of exploitation.
Audience: This course is designed for Texas physicians, nurses, social workers, pharmacy professionals, therapists, mental health counselors, and other members of the interdisciplinary team who may intervene in suspected cases of human trafficking and/or exploitation.
Additional Approvals: ABIM, ABS, ABA, ABP, ABO
Special Approvals: This course has been approved by the Texas Health and Human Services Commission (HHSC) to meet the requirement for human trafficking training.

Selected Course Availability List *(Cont'd)*

CHILD ABUSE IDENTIFICATION AND REPORTING: THE NEW YORK REQUIREMENT

#97533 • 2 Credits

By Mail – $23 • **ONLINE – $15**

Mandate: NY

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

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

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

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

INFECTION CONTROL: THE NEW YORK REQUIREMENT

#98643 • 5 Credits

By Mail – $33 • **ONLINE – $25**

Mandate: NY

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

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

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

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

PARKINSON DISEASE

#98772 • 10 Credits

Book By Mail – $58 • **ONLINE – $50**

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, ABO

ABIM CME MOC ACCREDITED

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

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

PART 2 MOC

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

MOCA

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

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

Successful completion of this CME activity, which includes participation in the evaluation component, enables the learner to satisfy the Lifelong Learning requirement for the American Board of Ophthalmology's Maintenance of Certification program. It is the CME activity provider's responsibility to submit learning completion information to ACCME for the purpose of granting MOC credit.

ROYAL COLLEGE
COLLÈGE ROYAL

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.

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

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

What You Should Know About…

Prostate Cancer Screening

Patient Education Handout
A service for patients

This page is perforated for easy removal.

UNDERSTAND the problem

Prostate cancer is a disease in which malignant (cancer) cells form in the tissues of the prostate. The prostate is a gland in the male reproductive system located just below the bladder and in front of the rectum. It is about the size of a walnut and surrounds part of the urethra (the tube that empties urine from the bladder). The prostate gland produces fluid that makes up part of semen.

As men age, the prostate may get bigger. A bigger prostate may block the flow of urine from the bladder and cause problems with sexual function. This condition is called benign prostatic hyperplasia (BPH), and although it is not cancer, surgery may be needed to correct it. The symptoms of benign prostatic hyperplasia or of other problems in the prostate may be similar to symptoms of prostate cancer.

WHO is at risk

Prostate cancer is the most common nonskin cancer among men in the United States. Prostate cancer is found mainly in older men. In the United States, about one out of every 8 men will be diagnosed with prostate cancer. Most men diagnosed with this disease do not die from it, but prostate cancer causes more deaths in men than any other cancer except lung cancer. Prostate cancer occurs more often in African American men than in White men. African American men with prostate cancer are more likely to die from the disease than White men with prostate cancer. The following risk factors may increase the risk of prostate cancer:

- Age
- Family history of prostate cancer
- Race
- Hormones
- Vitamin E
- Folic acid
- Dairy and calcium

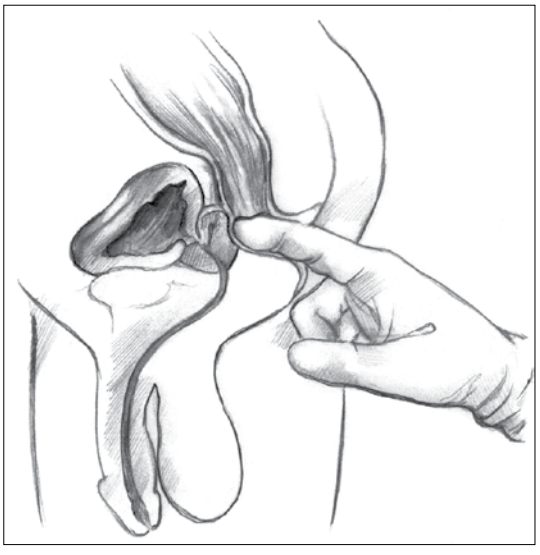
WHAT are the screening tests

Tests are used to screen for different types of cancer when a person does not have symptoms. Cancer screening trials also are meant to show whether early detection helps a person live longer or decreases a person's chance of dying from the disease. For some types of cancer, the chance of recovery is better if the disease is found and treated at an early stage.

Although there are no standard or routine screening tests for prostate cancer, the following tests are being used or studied to screen for it: digital rectal exam (DRE), prostate-specific antigen (PSA) test, and genetic testing. A PSA test or a DRE may be able to detect prostate cancer at an early stage, but it is not clear whether early detection and treatment decrease the risk of dying from prostate cancer.

Digital Rectal Exam

Digital rectal exam (DRE) is an exam of the rectum. The doctor or nurse inserts a lubricated, gloved finger into the lower part of the rectum to feel the prostate for lumps or anything else that seems unusual.



Source: National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Health.

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Prostate-Specific Antigen Test

A prostate-specific antigen (PSA) test is a test that measures the level of PSA in the blood. PSA is a substance made mostly by the prostate that may be found in an increased amount in the blood of men who have prostate cancer. The level of PSA may also be high in men who have an infection or inflammation of the prostate or benign prostatic hyperplasia (BPH).

Genetic Testing

A prostate cancer gene 3 (*PCA3*) RNA test may be used for certain patients. If a man had a high PSA level and a biopsy of the prostate did not show cancer and the PSA level remains high after the biopsy, a *PCA3* RNA test may be done. This test measures the amount of *PCA3* RNA in the urine after a DRE. If the *PCA3* RNA level is higher than normal, another biopsy may help diagnose prostate cancer.

WHO should be screened

The U.S. Preventive Services Task Force (USPSTF) recommends that men who are 55 to 69 years old should make individual decisions about being screened for prostate cancer with a PSA test. Before making a decision, men should talk to their doctor about the benefits and harms of screening for prostate cancer, including the benefits and harms of other tests and treatment. In general, men who are 70 years old and older should not be screened for prostate cancer routinely.

These recommendations apply to men who—

- Are at average risk for prostate cancer.
- Are at increased risk for prostate cancer.
- Do not have symptoms of prostate cancer.
- Have never been diagnosed with prostate cancer.

Other organizations may have other recommendations.

If you are thinking about being screened, you and your doctor should consider—

- If you have a family history of prostate cancer.
- If you are African American.
- If you have other medical conditions that may make it difficult for you to be treated for prostate cancer if it is found, or that may make you less likely to benefit from screening.
- How you value the potential benefits and harms of screening, diagnosis, and treatment

WHERE to get more information

National Cancer Institute

https://www.cancer.gov/types/prostate/patient/prostate-screening-pdq

Centers for Disease Control and Prevention

https://www.cdc.gov/cancer/prostate/basic_info/get-screened.htm

American Cancer Society

https://www.cancer.org/cancer/prostate-cancer/detection-diagnosis-staging/detection.html

This information is reprinted from material provided by the National Cancer Institute and the Centers for Disease Control and Prevention.

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- ☐ Mail - Add $6 for shipping & handling

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Complete after June 30, 2023, pay $150

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Complete all three courses or any combination of these three courses for a maximum payment of $104 (or pay the individual course price).

✓	Course #	Course Title / Credits	Price
	95500	Opioid Safety: Balancing Benefits and Risks / 5 Credits	$25
	98883	Sleep Disorders / 10 Credits	$50
	93764	Men's Health Issues / 15 Credits	$75

Additional Courses Available by Mail (Access Online for a Discount!)
Payment must accompany this form. To order by phone, please have your credit card ready.

✓	Course #	Course Title / Credits	Price
☐	40953	Moderate Sedation / 5	$33
☐	41473	Risk Management / 5	$33
☐	90471	Safe Clinical Use of Fluoroscopy / 10	$58
☐	90782	Colorectal Cancer / 15	$83
☐	91602	Opioids & Preventing Drug Diversion: The WV Req. / 3	$23
☐	91724	What Healthcare Prof. Should Know About Exercise / 5	$33
☐	91743	Child, Adolescent, & Adult Immunization Schedules / 5	$33
☐	95131	Prescription Opioids & Pain Mgmt: TN Guidelines / 2	$23
☐	96153	Alzheimer Disease / 15	$83
☐	96313	Human Trafficking and Exploitation / 5	$33
☐	96441	Suicide Assessment and Prevention / 6	$38
☐	96690	Anxiety Disorders in Older Adults / 3	$23
☐	96790	Psychedelic Medicine & Interventional Psychiatry / 10	$58
☐	96973	Cannabis and Cannabis Use Disorders / 5	$33
☐	97000	Implicit Bias in Health Care / 3	$23
☐	97022	Sexual Assault / 3	$23
☐	97081	Sexual Harassment Prevention: The IL Req. / 1	$23
☐	97383	Palliative Care and Pain Management at the EOL / 15	$83
☐	97470	Human Trafficking and Exploitation: The TX Req. / 5	$33
☐	97533	Child Abuse Identification & Reporting: The NY Req. / 2	$23
☐	98643	Infection Control: The New York Requirement / 5	$33
☐	98772	Parkinson Disease / 10	$58

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Subtotal
Expedited Delivery
Do not include Sales Tax $ 0
(Applicable sales tax is included for sales made to California addressees.)
Grand Total

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Answer Sheet

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Please note the following:

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

#95500 OPIOID SAFETY: BALANCING BENEFITS AND RISKS—5 CREDITS Please refer to pages 21–22.

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

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

#98883 SLEEP DISORDERS—10 CREDITS Please refer to pages 53–54.

Expiration Date: 12/31/24 *May be taken individually for $50*

	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.	❍	❍	❍	❍

#93764 MEN'S HEALTH ISSUES—15 CREDITS Please refer to pages 103–105.

Expiration Date: 06/30/25 *May be taken individually for $75*

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

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Evaluation

(Completion of this form is mandatory)

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To receive continuing education credit, completion of this Evaluation is mandatory.

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?

#95500
5 Credits

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

#98883
10 Credits

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

#93764
15 Credits

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

#95500 Opioid Safety: Balancing Benefits and Risks — If you answered YES to question #12, how specifically will this activity enhance your role as a member of the interdisciplinary team? _____

_____

_____

#98883 Sleep Disorders — If you answered YES to question #12, what change(s) do you plan to make in your practice? _____

_____

_____

_____

#93764 Men's Health Issues — If you answered YES to question #12, how specifically will this activity enhance your role as a member of the interdisciplinary team? _____

_____

_____

_____

Signature _____

Signature required to receive continuing education credit.

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Additional Course Order Form

(Refer to pages 106–110)

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State _____ License # _____ Exp. _____

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Date of Birth (Required for ABIM, ABS, ABA, ABP, ABPath, ABO Reporting) ___/___/___ (mm/dd/yyyy)

License Type: (circle one) MD / PA / DO / OPA / AA / Other: _____

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City _____ State _____ Zip _____

Phone ( ) _____

Fax Number ( ) _____

Email _____

(Incomplete information may delay processing.)

Please transfer your selected courses from pages 106–110 to this form.

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

Course #	Credits	Price	Course #	Credits	Price	Course #	Credits	Price
Sub Total		**$**	**Sub Total**		**$**	**Sub Total**		**$**
						Total Price		**$**

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Signature _____

Expedited mail delivery (within 2 to 3 days) is available in most areas at an additional charge of $35.

Call for information on international delivery.

Additional Courses _____

Subtotal _____

Expedited Delivery _____

Do not include Sales Tax $ 0
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Vol. 148
No. 4
MIMD23

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