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Geriatric Polypharmacy

Audience
This course is designed for advanced practice nurses, nurses, and allied healthcare professionals who work with the geriatric population.

Course Objective
The purpose of this course is to provide nurses in all practice settings the knowledge necessary to ensure that geriatric patients are effectively treated while reducing unnecessary polypharmacy.

Learning Objectives
Upon completion of this course, you should be able to:
1. Define polypharmacy in the elderly patient.
2. Identify guidelines to prevent the use of unnecessary medications in elderly patients.
3. Describe physiologic changes of aging that cause differences in drug metabolism.
4. Discuss the potential problems polypharmacy may cause in older patients.
5. Evaluate the impact of polypharmacy in specific conditions as well as approaches to avoid inappropriate prescribing.
6. Describe a prescribing cascade and the importance of medication assessment and reconciliation.

Faculty
Susan Waterbury, MSN, FNP-BC, ACHPN, entered the medical field as an RN in 1990. She continued her education, achieving a Master's Degree from the University of Central Florida in 1999. She has worked as a Family and Geriatric Nurse Practitioner since 2000, in family practice, geriatrics, hospice, and palliative care. She achieved board certification as a Family Nurse Practitioner in 2000 and as an Advanced Certified Hospice and Palliative Care Nurse in 2006. She holds nurse practitioner licenses in Florida, Virginia, and Maryland.

In addition to her clinical positions, Ms. Waterbury continues to play an active role in educating and mentoring nurses and other healthcare professionals. She is a faculty member of University of Phoenix, focusing on nursing leadership. She has developed and presented many educational programs for a variety of healthcare organizations and community groups.

Faculty Disclosure
Contributing faculty, Susan Waterbury, MSN, FNP-BC, ACHPN, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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

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This course represents an educational model that promotes the importance of learning objectives and individualized learning. Study questions will appear throughout the course to create a link between the learning objectives and the supporting text.

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

The elderly population of the United States is projected to grow substantially over the coming decades, comprising 20% of the total population by 2050 [1]. The population of those 85 years of age and older (referred to as the oldest-old) is expected to increase from 5.9 million in 2012 to 14.1 million by 2040 [1]. As a result, the number of older adults with multiple chronic illnesses requiring drug therapy will also increase significantly. The presence of chronic illness is a predictor of greater utilization of healthcare services, including nursing facility residence, and greater number of medications. Older patients and residents of nursing facilities may have more than 20 daily medications prescribed, and polypharmacy in the elderly is a serious problem that healthcare providers can evaluate and address to improve outcomes.

Hazards of polypharmacy include lack of adherence, overtreatment, adverse drug reactions, and incorrect dosage and administration regimens. Older patients may receive health care from a diverse set of providers, specialists, and consultants—often, one for each disease process. Each provider may prescribe additional medication(s), and as the number of medications increases, so does the risk of adverse drug reactions. In some cases, there is confusion regarding the proprietary (brand) and generic names of medications, with some patients taking a generic and brand version of the same drug. The increasing complexity of medication regimens leaves patients vulnerable to the hazards of polypharmacy and adverse drug reactions.

There is an increased demand for healthcare providers who are knowledgeable in geriatric prescribing practices. Specialized prescribing practices, geared toward managing multimorbidity in elders, are mandated by best practices and standards for geriatric care. Confusion about medication regimens, duplicate medications, non-adherence, and errors in self-administration make older adults at high risk for problems. In many cases, the “brown bag” approach is used to assess all the prescription and non-prescription medications the patient takes. This involves the patient bringing all prescription and over-the-counter medications he or she takes to each office visit. The patient/caregiver can then describe how the medications are taken/given and any reminder system or assistive device used (such as a medicine box/planner) to ensure compliance. Patient education and communication with primary care providers are key components of comprehensive care. Patients should understand that over-the-counter drugs, supplements, and home remedies are not inherently “safe” and have the potential for serious adverse effects or interactions.

Prescribers should also be aware of financial constraints experienced by many older adults, some of whom may be faced with the decision to buy either food or medications. In an effort to cut costs, these patients may decide to take a daily medication every other day or cut pills in half. Some may choose to take one medication over another based on their personal priorities (e.g., stopping an antihypertensive but continuing a hypnotic because they place a higher priority on getting good sleep).

Geriatric practitioners should have a comprehensive understanding of the physiologic changes of aging that occur, particularly in the liver and kidneys. Physiologic changes of aging cause differences in the absorption, distribution, metabolism, and excretion of medications. This increases the risk for adverse drug reactions or interactions due to excess drug accumulation and/or reduced clearance.

Today, older healthcare consumers or their representatives are often informed and savvy and may request every treatment available. They may demand a treatment a neighbor or relative was prescribed, or one that was advertised on television. Some patients may fall prey to online scams to purchase fraudulent products or supplements.

A formal drug re-evaluation should be performed regularly for all elderly patients. Providers should continuously assess prescribed drug therapies for necessity and appropriateness according to the patient’s goals of care and best evidence-based geriatric practices. Multiple medications may be necessary to treat comorbid conditions, but vigilance is required to monitor for adverse reactions or interactions.

Healthcare costs associated with the improper and unnecessary use of medications exceeded $200 billion in 2012, according to estimates from the IMS Institute for Healthcare Informatics [2]. These costs are related to adverse drug reactions or interactions, hospital admissions, emergency department visits, and outpatient care.

Reducing the number of medications older patients take is associated with reduction in mortality rates, improved quality of life, and reduced costs [3]. Medication regimen simplification is a priority to improve patient outcomes and reduce errors.
POLYPHARMACY DEFINED

How is polypharmacy defined?
The term polypharmacy is often used but not well defined. There are varied definitions in medical literature, but in general, polypharmacy has been defined as a single patient taking more than 5 drugs every day, with excessive polypharmacy defined as the prescription of 10 or more daily medications [3]. Polypharmacy may be used to describe excessive or unnecessary medications, inappropriate prescribing, or excessive use, overlap, or duplication of medications. There has been a call to redefine polypharmacy beyond an arbitrary number of medications [14]. In some cases of multimorbidity and chronic conditions (e.g., hypertension), the use of multiple medications may be the best practice according to clinical guidelines; this may be referred to as “appropriate polypharmacy” [15]. However, even when the prescription of multiple medications is warranted, it raises the risks of drug interactions, compliance issues, and adverse effects. Generally, the term polypharmacy has a negative connotation and is associated with the co-prescribing of potentially inappropriate medications.

IDENTIFICATION OF PROBLEMATIC MEDICATIONS IN THE ELDERLY

A retrospective study examined the use of potentially inappropriate medication use in older inpatients, and researchers found that 49% of elderly inpatients received at least one potentially inappropriate medication [6]. Care by a geriatrician and clinical Pharmacist intervention have been found to decrease potentially inappropriate prescribing practices for these patients [6]. Several tools have also been developed to help prescribers make the best selection of agents and minimize the risks of problematic polypharmacy in older patients.

THE BEERS CRITERIA

Which medications should be avoided in older adults due to the risk of Clostridium difficile infection and bone loss and fractures?

In older adults, certain drugs are considered inappropriate when the adverse pharmacodynamics, pharmacokinetics, and/or risk of drug interactions outweigh the potential benefits. In 1991, Mark H. Beers, MD, and his colleagues established a list of medications considered potentially inappropriate for patients 65 years of age or older. Known as the American Geriatrics Society (AGS) Beers criteria (Table 1), the resource was designed to educate prescribers, improve prescribing practices, and enhance quality assurance. Prescribers should review the medication regimen and determine the medical necessity of each drug the patient takes. The Beers criteria list continues to be updated (most recently in 2015) and used to guide and evaluate prescribing practices in geriatric patients. Notable new inclusions to the 2015 update of the list are proton-pump inhibitors, meclizine, and desmopressin [4].

The Beers list separates potentially inappropriate medications into several categories according to the strength of the recommendation and the potential adverse event. The first category includes drugs that are “potentially inappropriate” due to a higher risk of adverse effects and/or reduced efficacy in older patients; the AGS recommends that prescribers consider avoiding these agents [4]. The second category is for medications used in the treatment of common health problems (e.g., heart failure, seizures) that may exacerbate comorbidities in older patients. The third category is for potentially inappropriate medications that should be used with caution (and perhaps increased monitoring) in elderly patients [4]. Finally, the AGS provides a list of medications with potentially clinically important non-anti-infective drug-drug interactions that should be avoided in older adults or should be decreased in dose in those with impaired kidney function. Careful consideration should be given when prescribing medications that are on the Beers list. The criteria are meant to support good clinical judgment [46]. If the listed medications are used, they should be prescribed at the lowest effective dose for the shortest duration possible.

STOPP

The Screening Tool of Older Persons’ potentially inappropriate Prescriptions (STOPP) criteria focus on the avoidance of potentially inappropriate prescribing in elderly patients experiencing acute illness [5]. This tool places a special focus on potential drug-drug interactions, duplicate drug class prescriptions, and techniques to minimize adverse drug reactions. Criteria are organized according to physiologic system, which may make the tool easier to use. STOPP is designed to be used in conjunction with the Screening Tool to Alert doctors to the Right Treatment (START) criteria, which provides guidance on the medications that are recommended for older patients with specific conditions/diseases (e.g., arthritis, depression) [18].

A 2016 study comparing the effectiveness of STOPP and the 2003 and 2012 Beers criteria in identifying potential adverse drug events (including hospitalizations and emergency department visits) found that STOPP was slightly more specific (though less sensitive) than either Beers criteria [41]. The authors of this study recommended using the Beers and STOPP tools together for the best predictive value.
### Examples from the 2015 American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults

<table>
<thead>
<tr>
<th>Therapeutic Category (Drugs)</th>
<th>Rationale</th>
<th>Recommendation</th>
<th>Quality of Evidence</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-generation antihistamines (brompheniramine, carbinoxamine, chlorpheniramine, clemastine, cyproheptadine, dexbrompheniramine, dexchlorpheniramine, dimenhydrinate, diphenhydramine [oral], doxylamine, hydroxyzine, meclizine, promethazine, tripolidine)</td>
<td>Highly anticholinergic; clearance reduced with advanced age, and tolerance develops when used as hypnotic; risk of confusion, dry mouth, constipation, and other anticholinergic effects or toxicity. Use of diphenhydramine in situations such as acute treatment of severe allergic reaction may be appropriate.</td>
<td>Avoid</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td>Anti-infective (nitrofurantoin)</td>
<td>Potential for pulmonary toxicity, hepatotoxicity, and peripheral neuropathy, especially with long-term use; safer alternatives available.</td>
<td>Avoid in individuals with creatinine clearance &lt;30 mL/min or for long-term suppression of bacteria.</td>
<td>Low</td>
<td>Strong</td>
</tr>
<tr>
<td>Antiarrhythmic (digoxin)</td>
<td>Use in atrial fibrillation: Should not be used as a first-line agent in atrial fibrillation, because more-effective alternatives exist and it may be associated with increased mortality. Use in heart failure: Questionable effects on risk of hospitalization and may be associated with increased mortality in older adults with heart failure; higher dosages not associated with additional benefit and may increase risk of toxicity. Decreased renal clearance of digoxin may lead to increased risk of toxic effects; further dose reduction may be necessary in patients with stage 4 or 5 chronic kidney disease. If used for atrial fibrillation or heart failure, avoid dosages &gt;0.125 mg/day.</td>
<td>Avoid as first-line therapy for atrial fibrillation. Avoid as first-line therapy for heart failure.</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td>Antipsychotics (first- [conventional] and second- [atypical] generation)</td>
<td>Increased risk of cerebrovascular accident (stroke) and greater rate of cognitive decline and mortality in persons with dementia. Avoid antipsychotics for behavioral problems of dementia or delirium unless nonpharmacological options (e.g., behavioral interventions) have failed or are not possible and the older adult is threatening substantial harm to self or others.</td>
<td>Avoid, except for schizophrenia, bipolar disorder, or short-term use as antiemetic during chemotherapy.</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
</tbody>
</table>

*Table 1 continues on next page.*
## Examples from the 2015 American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults (Continued)

<table>
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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants, alone or in combination (amitriptyline, amoxapine, clomipramine, desipramine, doxepin &gt;6 mg/day, imipramine, nortriptyline, paroxetine, protriptyline, trimipramine)</td>
<td>Highly anticholinergic, sedating, and cause orthostatic hypotension; safety profile of low-dose doxepin (≤6 mg/day) comparable with that of placebo</td>
<td>Avoid</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td>Insulin, sliding scale</td>
<td>Higher risk of hypoglycemia without improvement in hyperglycemia management regardless of care setting; refers to sole use of short- or rapid-acting insulins to manage or avoid hyperglycemia in absence of basal or long-acting insulin; does not apply to titration of basal insulin or use of additional short- or rapid-acting insulin in conjunction with scheduled insulin (i.e., correction insulin)</td>
<td>Avoid</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td>Proton-pump inhibitors</td>
<td>Risk of <em>Clostridium difficile</em> infection and bone loss and fractures</td>
<td>Avoid scheduled use for &gt;8 weeks unless for high-risk patients (e.g., oral corticosteroids or chronic NSAID use), erosive esophagitis, Barrett esophagitis, pathological hypersecretory condition, or demonstrated need for maintenance treatment (e.g., due to failure of drug discontinuation trial or H2 blockers)</td>
<td>High</td>
<td>Strong</td>
</tr>
</tbody>
</table>

Source: [4] (Table 1)
CASE STUDY

Patient A is 82 years of age with a history of congestive heart failure, glaucoma, hypertension, and osteoarthritis. Her current medications are furosemide, potassium, lisinopril, metoprolol, aspirin, timolol maleate ophthalmic solution (Timoptic), acetaminophen (as needed), multivitamin, and a calcium/vitamin D supplement (800 IU daily). She has an appointment with a new orthopedic physician. During the appointment, the patient complains of persistent arthritic pain in her knee. The physician prescribes the NSAID meloxicam (7.5 mg per day) for pain and inflammation.

Comments and Discussion: From the orthopedic standpoint, prescription of meloxicam is good practice, as it should help to ameliorate patient A’s symptoms. However, from a cardiac standpoint, this is a risky approach due to the potential side effect of fluid retention and its effect on the heart. In general, NSAIDs can be dangerous for an individual of Patient A’s age. NSAIDs (including meloxicam, but also over-the-counter options like ibuprofen) have been issued “black box” warnings by the U.S. Food and Drug Administration for the increased risk of [45]:

- Serious and potentially fatal cardiovascular and thrombotic events, including myocardial infarction and stroke
- Serious adverse gastrointestinal events such as bleeding, ulcer, and intestinal perforation (higher in elderly patients)

Patient A has a good working relationship with her primary care provider, who has instructed her to contact him regarding any changes in her medication regimen. She calls her physician prior to taking the medication, and he advises her not to take the NSAID. Instead, he devises a pain management plan that minimizes the potential risks. Previously, Patient A was taking acetaminophen as needed, averaging up to one dose daily. This is increased to twice daily extended-release acetaminophen (650 mg). For breakthrough pain, tramadol 25 mg every four hours (as needed) is prescribed. Another option considered was the topical anti-inflammatory diclofenac sodium 1% topical gel, which would have fewer side effects than systemic agents. Aside from pharmacotherapy, the patient is scheduled with a physical therapist to create a safe exercise plan, including strengthening and range-of-motion exercises.

AGE-RELATED PHYSIOLOGIC CHANGES

What enzyme is the most important factor in the first phase of drug metabolism?

Aging is a complex process with variable effects resulting from a combination of heredity, the environment, comorbidity, diet, exercise, and culture. Although the rate by which one ages is unique, there are universal changes that occur in the body as one gets older, and these changes can affect the pharmacokinetics and pharmacodynamics of prescribed and over-the-counter medications.

Pharmacokinetic processes altered in aging include absorption, first-pass metabolism, bioavailability, distribution, protein binding, and renal/hepatic clearance. Age-related physiologic factors that may affect the absorption of drugs include delayed emptying time of the stomach, altered pH of the stomach contents, and slowed gastrointestinal tract motility. Changes in these processes begin with alterations in the functioning of individual cells.

In older patients, cells become less efficient at performing necessary functions. This may be the result of atrophy, hypertrophy, hyperplasia, dysplasia, and neoplasia. Atrophy is the shrinkage of cells and is most commonly noted in the brain, heart, skeletal muscle, and reproductive organs. It may result in dementia or contracture. In some cases, cells enlarge due to an increase of proteins in cell structures; this is referred to as hypertrophy. It has been hypothesized that this change may be a compensatory mechanism in response to atrophied cells. Hypertrophic changes in older patients may result in cardiomegaly or benign prostatic hypertrophy. Similarly, older patients are at increased risk for hyperplasia, or the increased reproduction of cells. This overgrowth of cells may lead to the development of benign growths (e.g., focal nodular hyperplasia, sebaceous hyperplasia) or it may be a precursor to cancer. Dysplasia is also more common in older adults. This is characterized by mature cells becoming disorganized and abnormal in size and/or shape. This is often a first stage in the development of neoplasia, or the new growth of benign or cancerous tumors.

These changes at the cellular level can affect the overall systemic metabolism of medications and/or may result in changes in the organs involved in metabolizing and eliminating medications. Specifically, the liver, kidneys, and gastrointestinal tract may reflect cellular changes through loss of function.
The functioning of the liver plays a significant role in the metabolism of drugs. The liver is the major site of drug transformation and elimination, and drugs administered by the oral route must pass through the liver prior to reaching systemic circulation. The enzyme cytochrome P-450 (CYP-450) is the most important factor in the first phase of drug metabolism, and this enzyme is primarily expressed in the liver. However, the liver's capacity to metabolize medications (and toxins) with CYP-450 is reduced by at least 30% in older patients [19]. In addition, the liver undergoes structural and microscopic changes with aging (e.g., reduced blood flow), and liver damage is repaired more slowly. As such, the metabolism of substances by the liver decreases, causing reduced inactivation of medications. This places older adults at increased risk for side effects due to reduced clearance of medications, which can be potentiated by the presence of hepatic disease. In many cases, elderly patients require reduced doses to adjust for these changes.

Age- and illness-related declines in kidney function necessitate dosage adjustments and possibly avoidance of certain medications. Renal elimination is a common form of drug excretion, and the rate by which medications are cleared lengthens with age. This can extend the action of drugs that undergo renal elimination, including morphine, heparin, lisinopril, and furosemide. Even with kidney changes, decreased muscle mass and limited physical activity can maintain serum creatinine levels within normal limits [19]. This can be misinterpreted as a sign of normal kidney function despite deficits. As such, caution is required when prescribing to elderly patients even when kidney function appears normal.

The Hartford Institute for Geriatric Nursing recommends that renal function should be assessed using Cockroft-Gault formula prior to administering renalclearing drugs. (http://www.guideline.gov/content.aspx?id=43938. Last accessed February 12, 2016.)

Level of Evidence: Expert Opinion/Consensus Statement

POTENTIAL PROBLEMS PRESCRIBING IN GERIATRICS

Prescribing to geriatric patients can be complex, and there are a number of factors that should be considered every time a new medication is considered. The prescribing problems that arise in this patient population may be generally categorized as problems of selection, interaction, or dosage. Many of these issues can be avoided if extra care is taken to evaluate the patient and his or her medical and medication history and provide better patient/caregiver education on adherence to prescription medication regimens. Issues specific to geriatric patients that should be included in the decision to prescribe a medication include the presence of comorbidities, life expectancy, redundancies, and the likelihood of compliance.

Older adults often have multiple conditions, the treatment of which may call for several medications. This potentially necessary polypharmacy can quickly escalate to be a burden on patients and/or their caregivers. The use of multiple medications has been associated with decreased adherence due to cost, complexity of regimens, and burnout. If possible, steps should be taken to limit the number of medications to those most effective for the patient. If a single medication may be of benefit for more than one of a patient's conditions, it should be preferred over multiple agents. Selecting the appropriate medication(s) for geriatric patients is made even more complicated by the lack of clinical guidelines and completed research focusing on this population.

Due to age-related physiological changes, elderly patients may be both more likely to experience adverse effects and less likely to derive a therapeutic benefit from a medication. This is compounded in patients with limited life expectancies. Life expectancy may be shorter than the time required to derive a benefit from a particular medication or treatment. The success of preventive treatment generally requires longer duration of treatment, and for patients with life-limiting conditions, preventive approaches may have little benefit. If the time to benefit from a certain drug is longer than the patient is expected to live, it should be avoided. Maintenance of quality of life and functional status become prime objectives.

Healthcare providers should perform a comprehensive review of patients' medication regimens, identifying any potential interactions or redundancies. Simplification is a priority to improve outcomes and reduce errors. If errors or inconsistencies are identified, further steps should be taken to avoid adverse reactions. Tapering or reducing medications may be indicated if a patient's condition has improved, stabilized, or resolved. The potential risks of pharmacotherapy may not be fully understood by patients and/or caregivers, so they may be reluctant to avoid or stop medications. Improved patient education is indicated in these cases.
With the development of new options for life-prolonging treatments and drugs comes a potential for an increased burden of treatment as well. Burdens of treatment include adverse drug reactions and/or interactions, overtreatment, non-adherence, medication errors, and cost. Focusing on quality-of-life issues, functional status, and preferences may be a better approach than aggressive attempts to reach target goals.

Evaluating and treating patients with polypharmacy requires a good working relationship and communication. Patients and caregivers require education about over-the-counter medications and supplements that may be dangerous and should be avoided. Some patients and their caregivers may require adaptive approaches to understand and adhere to the prescribed regimen. This includes ensuring that patients who use assistive devices (e.g., glasses, hearing aids) are using these tools. When appropriate, alternative communication approaches (e.g., large-print text, an interpreter) may be used. Education regarding medications should be provided in a quiet environment, free of distraction. Teaching may include repeated instructions in a stepwise fashion, with visual reinforcements and a return demonstration for functional tasks.

NURSING HOME REGULATIONS

What do the Centers for Medicare and Medicaid Services (CMS) regulations state regarding the use of medications for nursing facility residents?

More than 3 million Americans receive care in skilled nursing facilities each year, and 1.4 million Americans reside in nursing homes [7]. The Centers for Medicare and Medicaid Services (CMS) work to promote nursing home quality improvement, address reimbursement issues, and ensure compliance with CMS-defined best practices. Nursing facilities are required to comply with CMS regulatory requirements in order to receive payments under the Medicare or Medicaid programs.

CMS regulations state that nursing facility residents should only receive medications when the potential benefits outweigh the risks or burden of treatment [12]. There must be a clear clinical indication and diagnosis for any medication, and prescribed medications should be given for the proper duration at the correct dose. State surveyors review patients’ medication regimens to assess for unnecessary medications. If a patient is found to have been prescribed an unnecessary drug, the facility may receive a citation (referred to as F-Tag 329) for violating the CMS requirement to avoid unnecessary medications. In 2015, CMS issued a memo indicating that surveyors have been trained to increase investigations for unnecessary drugs, particularly antipsychotic medications in the management of dementia [20]. This regulation is intended to help promote or maintain the patient’s highest functional, emotional, and physical level of wellness. To comply with F329, each patient’s drug regimen should be monitored on a regular basis, with goals of treatment identified. Only drugs that are medically necessary should be administered in the correct dosages and for only the clinically indicated duration. After a medication has been ordered, the patient should be monitored for therapeutic response, adverse reactions, interactions, and necessity of ongoing treatment. Any significant decline in functional or physical status should be immediately correlated with any new drugs or changes in drug dosages. Significant declines in status should be recognized and evaluated, with adjustment of the medication regimen if warranted.

CASE STUDY

Patient B is a man, 78 years of age, who resides in a nursing facility. One year ago, he fell and fractured his left hip and underwent surgical repair. He returned to the nursing facility, completed rehabilitation, and regained most of his prior function. After the surgery, Patient B was prescribed warfarin to prevent deep venous thrombosis (DVT) after surgery.

During a routine survey, a state surveyor discovers that Patient B is still being administered warfarin. After further investigation, it is discovered that the warfarin was never discontinued after the appropriate duration after the hip fracture repair. The surveyor considers warfarin an unnecessary drug, and a citation (F-Tag 329) is issued. After contacting the attending physician, the warfarin is promptly discontinued.

Comments and Discussion: Patient B’s case is an example of using the right drug but not using it for the correct duration. After orthopedic surgery, warfarin is usually indicated for approximately two to three months or until activity/ambulation has increased to a point that the risk of DVT is reduced. There is a substantial burden of treatment with warfarin, including weekly evaluations of prothrombin time/international normalized ratio (PT/INR), adverse reactions, interactions, and increased risk of bleeding and brain hemorrhage, especially for patients with a history of falls.

There is shared responsibility for this error between the prescriber/healthcare provider and the facility. The provider did not follow through and discontinue the medication when it was no longer needed, and the facility nursing staff should have realized that the drug was no longer necessary and approached the provider for an order to discontinue. The nursing facility could have called the orthopedic physician for orders and duration of warfarin treatment after surgery. When a medication is started, the stop date for that medication should be considered and established. The consultant pharmacist could have intervened as well.
ADVERSE DRUG REACTIONS

ADRs represent a significant economic burden to the healthcare system, causing an estimated 99,628 hospitalizations annually for older adults [9]. One-third of ADR-related hospitalizations involve warfarin, and another one-third involve insulin, other antiplatelet drugs, and oral hypoglycemics [9]. Anticoagulants, anticonvulsants, and digoxin are also commonly implicated in ADR-associated hospitalizations.

An ADR is a symptom, consequence, and/or injury that occurs due to the administration of a medication, causing a noxious, unintended, and/or undesired effect. A reaction is categorized as an ADR if it occurs at normal human doses for prophylaxis, diagnosis, and/or treatment. It may be a secondary effect of a drug that is undesirable and different from the therapeutic effect or may cause a functional decline or impairment in mental or physical functioning.

A retrospective study analyzing the costs and incidence of emergency department visits related to ADRs in patients 65 years of age or older identified the following risk factors [10]:

- Newly prescribed drugs
- Use of multiple pharmacies
- Multiple medications
- Recent hospitalization/ER visit
- Female gender
- Comorbidity
- Residence in a nursing facility

The subjects in the study had been prescribed an average of 12.9 medications in the year preceding emergency department admission.

A review of the National Mortality Statistics database for deaths due to adverse drug effects during clinical use found an increased incidence of death from ADRs in persons older than 55 years of age, with the highest risk occurring after 75 years of age [11]. Anticoagulants, opioids, and immunosuppressants were most commonly associated with an adverse effect resulting in death [11].

There are five major categories of ADRs: side effects, hypersensitivity, idiosyncratic response, toxic reactions, and adverse drug interactions. Side effects are secondary effects of a drug and may be dose related. Hypersensitivity to a drug is immunologically mediated. In severe cases, anaphylaxis may occur. An idiosyncratic response is an unusual or unexpected reaction. Toxic reactions are often related to the dose or duration of drug therapy. Less often, build-up of metabolites may precipitate a toxic reaction, as with digoxin or phenytoin toxicity.

The impact another drug or substance has on a medication is referred to as a drug-drug interaction. The interaction may alter drug metabolism, absorption, elimination, distribution, and/or pharmacokinetics. The intended effects of medications may be increased or decreased secondary to the interaction. In addition, undesired drug effects (e.g., exacerbation of a disease or condition) may develop in patients with certain disease states. For example, nonselective beta-blockers may induce bronchospasm in patients with asthma. These drug-disease interactions may be more common in older patients with multiple comorbidities.

Common ADRs include hypoglycemia, candidiasis, allergic reaction, gastrointestinal complications, hypotension, dysrhythmia, severe headache, dizziness, acute renal failure, and respiratory complications. Each patient has the potential for a unique reaction to a medication and may be genetically predisposed to either have an increased or decreased reaction to a drug.

Specific therapies are associated with the increased potential for ADRs in older patient, even with adherence to treatment guidelines for the general adult population. Improved management of several drug classes, including antithrombotic and antidiabetic drugs, has been recommended to prevent ADRs in the elderly [9]. Heparin, aspirin, and clopidogrel have all been associated with adverse bleeding events, including brain hemorrhage, hematuria, gastrointestinal bleeding, and hematoma [9]. Diuretics (e.g., furosemide, hydrochlorothiazide) may cause hyponatremia, azotemia, and falls in elderly patients. Decreased oral intake of food and fluids during illness may cause dehydration when combined with a diuretic. Urinary urgency and incontinence may cause older patients to engage in risky behavior to get to the bathroom, despite caregivers’ instructions to call for assistance. During times of illness, these medications may need to be held or dosages adjusted to respond to the patient’s change in condition.

Adverse reactions that lead to delirium or altered mental status most commonly occur after use of medications with sedation and antihistaminic effects. Confusion and delirium in elderly patients may occur secondary to opioid analgesics (e.g., morphine, oxycodone), anticonvulsants (e.g., phenytoin, valproic acid), sedatives (e.g., diazepam, alprazolam), hypnotics (e.g., temazepam, zolpidem), and antipsychotics (e.g., haloperidol, quetiapine).
ANTICOAGULANT THERAPY

As noted, adverse events associated with warfarin cause up to one-third of emergency department visits and hospitalizations among older adults [9]. As such, improved management of anticoagulants has the potential to significantly reduce morbidity and mortality in this population. First used in the 1950s, warfarin is considered the criterion standard for anticoagulation and is widely used to prevent and treat thrombosis and thromboembolism. Other indications for warfarin include atrial fibrillation, artificial heart valve, and pulmonary embolism. Dosing of warfarin is individualized and closely monitored by the INR, which measures serum viscosity. In general, INR should be between 2 and 3 in patients taking warfarin. For high-risk patients or those with prosthetic valves, the desired range may be 2.5–3.5, and older adults who are at high risk for complications may be maintained at 1.8–2.

The FDA has issued a black box warning for warfarin regarding the risk of major or fatal bleeding. This risk is increased in patients older than 65 years of age with high-intensity coagulation (i.e., INR >4), variable INR, and/or other comorbidities [45]. Frequent INR monitoring is recommended along with careful dosage adjustment. Warfarin is contraindicated in patients with active bleeding, gastrointestinal bleeding, hemorrhagic stroke, blood dyscrasias, recent surgery, a high risk for non-compliance, and moderate-to-severe hepatic impairment. Caution is recommended in patients older than 65 years of age and in patients with a history of falls due to the risk of subdural hematoma and severe or fatal bleeding.

Aside from the risk of serious bleeding, common adverse reactions to warfarin include bruising, abdominal pain, nausea, vomiting, fatigue, headache, dizziness, taste changes, dermatitis, and fever. Over-the-counter medications can also interact with anticoagulants. The anticoagulant effects of warfarin and the antiplatelet effects of clopidogrel can be enhanced by the simultaneous use of ibuprofen, with the potential for internal bleeding. While the adverse interaction of warfarin with aspirin and NSAIDs is common knowledge, the significant potential interaction between warfarin and acetaminophen is less well known. Liver metabolism, drug and food interactions, and genetic factors also affect the efficacy of warfarin. Vitamin K-rich foods, such as green leafy vegetables and soy, decrease the effect of warfarin, reducing the PT/INR to subtherapeutic levels. Patients should be advised to eat a consistent daily amount of these foods in order to maintain a constant INR.

The consumption of alcohol may also affect the action of warfarin. Acute alcohol intake of more than a few drinks increases the anticoagulant effects of warfarin and can lead to increased bleeding [42]. Conversely, chronic alcohol use is associated with increased warfarin metabolism and impaired anticoagulation. In general, patients who are taking warfarin should abstain from alcohol consumption or limit their intake to one or two servings of alcohol occasionally.

Other agents used for anticoagulation include heparin, low-molecular-weight heparin, rivaroxaban, and dabigatran, all of which require a very cautious approach when treating elderly patients. Close monitoring and follow-up over time are essential to improved outcomes. As patients age, their health and functional status may change, and providers should reassess patients for contraindications to anticoagulant therapy, including falls, gastrointestinal bleeding, and hemorrhagic stroke. These complications are life-threatening, and their risk may outweigh the potential benefit of anticoagulation, requiring the cessation of therapy. Another important consideration is the patient’s adherence to the prescribed therapy and regular blood testing. Patients should not be prescribed warfarin if they are not able to comply with monitoring requirements.

ANTIDIABETIC MEDICATIONS

Which factors in older patients with diabetes may lead to hypoglycemia unawareness?

The management of diabetes often requires the prescription of multiple medications for optimum control, and this coupled with multiple medical comorbidities and a lack of research focusing on geriatric patients can make treatment complex. The main goal of treatment of diabetes in the elderly is to decrease metabolic complications while maintaining functional status and quality of life. Individualized management is crucial.

Age-related changes in drug absorption, distribution, metabolism, and clearance should be considered in all older patients with diabetes. For frail patients, the risks of intensive glycemic control often outweigh the benefits. Elderly patients may have a variable dietary intake related to physical or mental illness. If a patient skips a meal because he or she feels ill but takes or is given the usual dosage of insulin (especially fast-acting insulin), hypoglycemia will occur. Even when adequate calories are consumed, the older adult's intestinal absorption of those calories is slowed. As a patient ages, the adrenergic response to low blood glucose diminishes or disappears. Additionally, the preliminary symptoms of hypoglycemia, including lack of motor skills and confusion, may be misdiagnosed or unrecognized [43]. This can result in hypoglycemia unawareness in elderly patients with diabetes, which can allow the condition to become more severe. Unawareness of hypoglycemia is associated with a six-fold and nine-fold increased risk of severe hypoglycemia in patients with type 1 and type 2 diabetes, respectively [44].
Risk factors for hypoglycemia include polypharmacy, chronic renal or hepatic impairment, poor nutrition, comorbidities, the use of insulin or sulfonylureas, and acute illness. The Beers criteria lists sliding-scale insulin as a potentially inappropriate medication for persons older than 65 years of age, with a higher risk of hypoglycemia without improvement in diabetic management regardless of care setting [4]. The preferred treatment for older patients who require insulin is a daily basal rate of long-acting insulin, such as insulin glargine or insulin detemir. As with other geriatric prescribing, it is important to start with a low dose and increase slowly. Weekly re-evaluation and close monitoring is required, especially when initiating insulin therapy in patients older than 60 years of age.

Oral hypoglycemics can have a rebound hypoglycemic effect in patients with decreased renal or hepatic function (including age-related changes), and sulfonylureas (e.g., glipizide, glyburide) should be used with caution in elderly patients or those who are debilitated or malnourished [45]. Metformin has a low risk of hypoglycemia, but its use in older patients may be limited by comorbid illnesses such as renal/hepatic dysfunction, congestive heart failure (CHF), or chronic obstructive pulmonary disease (COPD). Metformin begins to accumulate in the body when the glomerular filtration rate (GFR) is less than 50–60 mL/min/1.73 m². Therefore, as a patient ages and renal function declines, it may be necessary to initiate more frequent monitoring of renal function and/or reduce or discontinue metformin use. For geriatric patients, especially those older than 80 years of age, the risks and potential adverse effects of metformin may preclude its use. If it is used, reduced dosage (250–500 mg twice daily) should be considered along with close monitoring of renal function and monthly metabolic panels.

Intense diabetes treatment and tight glycemic control can have serious consequences in elderly patients [21; 22]. In the geriatric population, hypoglycemia is associated with an increased risk of myocardial infarction, functional decline, falls, and cognitive impairment. The AGS recommends a target glycated hemoglobin (HbA1c) of <8% for elderly patients with a longer duration of diabetes (more than 10 years) or comorbidities who require combination therapy, including insulin, to manage the disease [23]. When diabetes is aggressively managed using guidelines more appropriate for younger adults, older patients are at risk for hypoglycemia and other complications. When deciding whether to offer or continue treatment of diabetes for patients older than 70 years of age, the benefit/risk ratio should factor in comorbidities, cognitive status, ability to self-manage, life expectancy, and vulnerability to hypoglycemia [24].

Most hospitalized patients with diabetes will require bolus insulin before meals and at bedtime based on blood glucose monitoring. These orders will be included on the discharge medication list if the patient is discharged to a skilled nursing facility. However, patients with stable type 2 diabetes should transition away from the daily blood glucose testing and on-demand insulin routinely ordered for hospitalized patients. One approach is to continue the bolus insulin at mealtimes for seven days while discontinuing bedtime doses to reduce the risk of nocturnal hypoglycemia. After seven days, the amount of insulin required daily may be used to establish a daily long-acting insulin regimen.

For example, if a patient required 72 units of regular insulin in one week, an average daily dose of about 10 units may be used as a starting point for long-lasting insulin (i.e., 10 units subcutaneous insulin each day). While in the process of adjusting insulin dosages, re-evaluation every week is prudent. Patients with glucose spikes may require the addition of bolus insulin before meals.

It is important to consider how often patients are willing to self-monitor blood glucose and give themselves insulin. While a small percentage of patients/caregivers would comply with testing and coverage four times per day, this is not a realistic expectation for most patients. Patients may complain about the pain of fingersticks and frequent injections of insulin, and episodes of hypoglycemia may make patients feel ill for days and require emergency intervention/hospitalization. Reducing any unnecessary medications, treatments, and intervention creates good rapport and allows more time to focus on improving the patient’s quality of life.

**MANAGEMENT OF INSOMNIA**

Insomnia is a common complaint by elderly patients, causing many visits to primary care providers and psychiatrists. As a person ages, sleep patterns typically change. Increased sleep during the day causes a reduced need for sleep at night. There may be a perceived insomnia by the patient despite sleeping 7 hours or more in a 24-hour period. For patients with insomnia, providers should complete a comprehensive medical and psychological assessment to diagnose underlying conditions that may cause a sleep disorder, including an acute stressor (e.g., grief), chronic pain, sleep apnea, anxiety, depression, or alcohol/substance misuse. Diagnosis and treatment of underlying comorbidities may make pharmacotherapy unnecessary.

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. Sound sleep hygiene practices should be discussed with patients and/or caregivers, and willingness to undertake these and other nonpharmacologic options should be assessed and encouraged [16]. Exercise history should also be obtained, and
when levels are inadequate, exercise as treatment should be discussed. Increased physical activity has been shown to be as effective as benzodiazepines in improving sleep patterns in several studies [17]. Other nonpharmacologic treatment options include relaxation therapy and sleep restriction [17]. These are often first-line treatments due to the low cost, lack of side effects, and no risk of dependency. The use of over-the-counter sleep aids (especially those containing antihistamines) should be discouraged, as should the use of alcohol, due to marginal efficacy and reduction in sleep quality and because they may cause residual drowsiness and have the potential for dependency [17].

If medication is indicated to treat insomnia, the benzodiazepine temazepam (7.5 mg in older patients) is frequently used, as it is available in a generic form with a relatively low cost. According to the AGS Beers criteria, benzodiazepines are potentially inappropriate medications in the elderly and should be avoided if possible. Safer alternatives to temazepam include sedative-hypnotics (e.g., suvorexant) and melatonin. If a hypnotic is selected, it should be prescribed at a lower dose than for younger patients. Melatonin may be of benefit to a subset of patients with delayed sleep phase syndrome (a disturbance of the circadian rhythm), but it does not appear to be helpful for most people who have insomnia. It is safe when used in modest dosage (0.2–0.3 mg per night) for short periods (three months or less) [39]. Melatonin is unregulated by the U.S. Food and Drug Administration (FDA), so formulations vary in strength, and higher doses can lead to adverse side effects (e.g., disrupted sleep, fatigue, headache).

Another frequently used sleep aid is diphenhydramine, with multiple over-the-counter formulations available. Despite its widespread use, diphenhydramine is included on the Beers criteria as a potentially inappropriate medication in the elderly. Diphenhydramine is a first-generation antihistamine that is metabolized by the liver through the CYP-450 pathway. It non-selectively antagonizes central and peripheral histamine H1 receptors. It is a substrate/inhibitor, has a half-life of 3.4 to 9.2 hours, and is excreted in the urine. It has strong anticholinergic effects, which may cause constipation, dry mouth, impaired coordination, urinary retention, and hypotension. Drugs like this that have anticholinergic side effects may have a cumulative effect, leading to increased sedation or delirium. Drug-disease precautions include glaucoma, prostatic hypertrophy, asthma, COPD, and gastrointestinal obstruction. Tolerance may develop when used as a sleeping agent, causing reduced effect and resulting in patients increasing their dosages, with associated higher risks of adverse reactions. Caution is recommended when using this drug in elderly patients, especially those who take other central nervous system (CNS) depressants and/or anticholinergics. It should be avoided as a sleep aid in favor of better options.

The AGS also recommends that hypnotics (e.g., eszopiclone, zaleplon, zolpidem) should be avoided (without consideration of duration of use), particularly if any other CNS-active drugs are already prescribed. These drugs have adverse events in the elderly similar to benzodiazepines [4]. Liver impairment and concomitant alcohol use are relative contraindications. Again, prescribers should weigh the potential of a positive benefit to the patient versus the risk of an adverse event. After prolonged use, tapering of these medications is required to prevent withdrawal symptoms.

ANTIPSYCHOTIC MEDICATIONS IN LONG-TERM CARE

As noted, CMS regulations for long-term care facilities require antipsychotic drugs to be used only when necessary to treat a specific condition, as diagnosed and documented in the medical record and based on a comprehensive assessment of the resident [12]. The dosage of these medications should be gradually reduced until the lowest effective dose is established, unless clinically contraindicated. Of particular concern is the chemical restraint of elderly long-term care facility residents, which has resulted in increased scrutiny of psychotropic medication prescribing by state and federal regulatory agencies.

Typical (e.g., haloperidol, thioridazine) and atypical antipsychotics (e.g., olanzapine, risperidone) are considered dangerous when used in patients with dementia, and the FDA has issued a black box warning that elderly patients with dementia-related psychosis treated with antipsychotics are at an increased risk for death (mainly due to cardiovascular or infectious causes) compared with placebo [45]. In terms of liability, the burden of proof lays with providers and caregivers to provide the documentation that the medication is medically necessary.

Antipsychotic medications are used to treat psychosis associated with bipolar disorder, schizophrenia, agitation, delusions, dementia, and paranoia. However, before prescribing antipsychotic drugs, any medical or toxic causes of the behavior should be ruled out. A thorough patient history, physical examination, and laboratory studies (e.g., complete blood count, comprehensive metabolic panel, urinalysis, drug levels) are indicated for differential diagnosis.

For residents in long-term care facilities, nonpharmacologic methods of behavior control should be attempted and documented before antipsychotics are initiated. As with any treatment, a risk-benefit analysis should be performed, and the patient’s/caregiver’s agreement to use the drug should be documented (Table 2).
Healthcare providers should work to promote and maintain the independence and mobility of patients with dementia without relying on antipsychotics. The first step for those in skilled nursing facilities is maintaining consistent staffing. Additional interventions should focus on maximizing independent activity and enhancing function while adapting and developing skills and may include:

- Retaining a familiar environment
- Minimizing relocations
- Accommodating fluctuating abilities
- Obtaining assessment and care-planning advice regarding activities of daily living, toileting skills, and skill training from an occupational therapist
- Modifying the environment to aid independent functioning, including incorporating assistive technology, with advice from an occupational therapist and/or clinical psychologist
- Encouraging physical exercise, with assessment from physical, occupational, and speech therapists (when indicated)
- Specific therapeutic approaches (e.g., social worker/spiritual assessment, redirection, distraction, reality orientation, reminiscence therapy, art therapy, music therapy, bright-light therapy)

A prescribing cascade occurs when a patient has an ADR and additional drugs are prescribed to control the symptoms of this reaction (Figure 1). Adverse drug reactions should be vigilantly ruled out prior to diagnosing a new medical condition.

Prompt detection and correction of adverse drug reactions are essential to ensuring good outcomes. Changes in medications and dosages should serve as red flags when evaluating a potential new problem.

An example of a prescribing cascade involves the prescription of cholinesterase inhibitors (e.g., donepezil, rivastigmine, galantamine) for dementia and the secondary prescription of an anticholinergic (e.g., oxybutynin, tolterodine, flavoxate) for urinary incontinence. Cholinesterase inhibitors and anticholinergic drugs are considered to have opposing effects, and patients who receive a cholinesterase inhibitor have a significant increase in urinary incontinence, with the subsequent prescription of an anticholinergic agent for bladder control [8]. Even aside from potential drug-drug interactions, medications with anticholinergic side effects should be avoided in patients with dementia as they increase the risk for cognitive decline and delirium [12].
TRANSITIONS OF CARE

During a transition of care (i.e., when a patient moves from one site of health care to another) it is common for essential information not to be conveyed to the receiving care providers. It is vital for care transitions to be coordinated so each provider has a comprehensive view of the patient. Poor communication can result in duplication of services, waste of resources, and medication errors. Potentially and actually inappropriate medications for elderly patients are frequently prescribed in hospital and emergency department settings and continued after discharge [40]. Prescribers in these settings often fail to adhere to guidelines to modify prescribing practices for older patients [13].

MEDICATION RECONCILIATION

When should medication reconciliation be conducted?

Medication reconciliation is the process of creating and updating a current medication list as compared with any previous lists. This should be conducted:

- On admission
- During routine and acute visits by providers
- After transitions of care
- During significant change in condition
- When the goals of care change
- Before prescribing new medications
- When discontinuing any as-needed or routine orders
- When considering the risks, benefits, and burden of any prescription

Attempts to reduce or discontinue medications should be done selectively, one medication at a time. Medications may have been initially prescribed many years previously for a chronic condition, and newer agents with improved side effect profiles may be available. In some patients, addiction and dependence issues may arise. Regular comprehensive assessments of the patient are crucial, with the appropriate and necessary referrals made to psychiatry, psychology, addiction specialists, pain management, and other specialists as necessary. Certain medications should not be abruptly stopped and should instead be slowly reduced with medical supervision. This includes benzodiazepines (due to risk of...
symptoms of drug withdrawal), beta-blockers (due to risk of rebound cardiac symptoms), and corticosteroids (due to risk of adrenal crisis).

When a patient is transferred to the hospital, certain routine medications (e.g., anticholinesterase inhibitors) may be stopped. Therefore, it is important to review the pre-hospital medication regimen and compare it with the medication list provided by the hospital. If important omissions are found, they may need to be reordered.

In long-term care facilities, residents are visited by their primary care provider every 30 to 60 days. The medication regimen should be carefully reviewed and reconciled at each of these visits. Psychotropic drug meetings are conducted monthly and include the medical director, nursing director, a social worker, and a psychiatrist. The continued necessity of antipsychotic, antidepressant, and psychoactive medications should be reviewed for medical necessity and possible gradual dosage reductions. If further dosage reductions are clinically contraindicated, this should be documented on the progress note.

The Hartford Institute for Geriatric Nursing recommends that nurse practitioners, physician assistants, and/or physicians should review and record the total number of routine and as-needed medications at each periodic visit.


**Level of Evidence:** C-1 (evidence from observational studies with consistent results)

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**CASE STUDY**

Patient T is a man, 84 years of age, who resides in a long-term care facility. He has been diagnosed with congestive heart failure, hypertension, arthritis, and hyperlipidemia and has a history of two myocardial infarctions (eight and two years previously). He requires minimal assistance with his activities of daily living and remains ambulatory with a cane. His usual medications are:

- Metoprolol ER: 50 mg daily
- Aspirin: 325 mg daily
- Omeprazole: 20 mg daily
- Lisinopril: 10 mg daily
- Furosemide: 40 mg every day
- Potassium chloride: 20 mEq twice daily
- Atorvastatin: 20 mg daily
- Acetaminophen: 650 mg twice daily
- Tramadol: 50 mg, as needed
- Multivitamin

At baseline, he takes 10 medications/supplements.

Patient T is transferred to the emergency department for increased shortness of breath. He is diagnosed with bronchitis and spends 24 hours in the hospital for observation before being transferred back to the long-term care facility for ongoing care. At the care facility, the receiving practitioner reviews the medication list from the hospital:

- Levofoxacin: 500 mg daily
- Prednisone: 20 mg daily
- Tiotropium bromide, inhalation: 1 puff daily
- Levalbuterol tartrate, inhalation solution for nebulizer: As needed for shortness of breath
- Promethazine: 25 mg every six hours as needed
- Haloperidol: 1 mg every four hours as needed
- Bisacodyl: 10 mg every day as needed

Including the as-needed medications, Patient T is currently prescribed 17 drugs. Physical assessment reveals an elderly debilitated man who is in no acute distress (*Table 3*). He is alert and oriented and answers questions appropriately. His intake of food and fluids has been poor since his return from the hospital, and he is using oxygen per nasal cannula at 2 L/minute.

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**RESULTS OF PATIENT T’S PHYSICAL EXAM**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td>112/62 mm Hg</td>
</tr>
<tr>
<td>Temperature</td>
<td>97.8° F</td>
</tr>
<tr>
<td>Heart rate</td>
<td>92 beats per minute</td>
</tr>
<tr>
<td>Respiration rate</td>
<td>22 breaths per minute</td>
</tr>
<tr>
<td>Height</td>
<td>5 feet 9 inches (175 cm)</td>
</tr>
<tr>
<td>Weight</td>
<td>65.3 kg (144 pounds) (usual: 154 pounds)</td>
</tr>
<tr>
<td>Heart sounds</td>
<td>S1, S2 with 2/6 systolic ejection murmur</td>
</tr>
<tr>
<td>Lung sounds</td>
<td>Few expiratory wheezes noted anteriorly</td>
</tr>
<tr>
<td>Extremities</td>
<td>No significant edema</td>
</tr>
<tr>
<td>Abdomen</td>
<td>Unremarkable</td>
</tr>
</tbody>
</table>

*Source: Compiled by Author*  
*Table 3*
As noted, Patient T's new diagnosis is bronchitis, and he does not appear to be having an exacerbation of his CHF. The first step in medication reconciliation is to discontinue any as-needed medications ordered in the hospital that are no longer necessary. Haloperidol is frequently used to treat delirium in geriatric patients in the hospital setting, but it is considered inappropriate for this use in long-term care facilities. Secondly, duration should be established for levofloxacin and prednisone. The receiving practitioner contacts the ordering physician and determines the levofloxacin should be continued for seven days and the prednisone continued for two weeks with a plan for tapering to discontinue. A pulmonary consultation follow-up is scheduled in two weeks, the pulmonologist will determine the duration of the inhalation drugs started during the hospitalization. The oxygen therapy was also acquired during the hospitalization, and serial oxygen saturation readings will be used to determine whether Patient T will require long-term oxygen therapy.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Indication/Diagnosis</th>
<th>Potential Reduction</th>
<th>Considerations for Reduction or Discontinuation of Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol extended-release (50 mg daily)</td>
<td>Hypertension</td>
<td>No</td>
<td>If blood pressure or heart rate fall, or symptoms of orthostasis or hypotension occur, dosage reduction should be considered.</td>
</tr>
<tr>
<td>Aspirin (325 mg daily)</td>
<td>Heart disease</td>
<td>Yes</td>
<td>Lowest effective dose. Would 81 mg dose be as effective with less risk of gastrointestinal (GI) bleeding?</td>
</tr>
<tr>
<td>Omeprazole (20 mg daily)</td>
<td>Gastritis</td>
<td>Yes</td>
<td>Possibility that this may no longer be necessary if given for an acute episode. Consideration for GI prophylaxis related to steroids and/or aspirin.</td>
</tr>
<tr>
<td>Lisinopril (20 mg daily)</td>
<td>Congestive heart failure, hypertension</td>
<td>No</td>
<td>ACE inhibitor should be part of treatment plan for patients with congestive heart failure. Renal function must be monitored.</td>
</tr>
<tr>
<td>Furosemide (40 mg daily)</td>
<td>Congestive heart failure</td>
<td>Yes</td>
<td>Consideration of the lowest effective dose. During acute illness (except congestive heart failure), especially with dehydration, dose reduction or holding dose may be appropriate.</td>
</tr>
<tr>
<td>Potassium chloride (20 mEq [oral] daily)</td>
<td>Replacement</td>
<td>No</td>
<td>Potassium levels should be monitored, with adjustment of dose as required.</td>
</tr>
<tr>
<td>Atorvastatin (20 mg daily)</td>
<td>Hyperlipidemia</td>
<td>Yes</td>
<td>Limited evidence base for use of statins in patients older than 80 years of age. Comorbid heart disease is an important consideration. Monitoring of lipid levels and liver function levels guides treatment.</td>
</tr>
<tr>
<td>Acetaminophen (650 mg [oral] twice daily)</td>
<td>Arthritis</td>
<td>No</td>
<td>1,300 mg of acetaminophen daily is well below the maximum recommended dose. Caution when used with alcohol or other drugs metabolized by the liver.</td>
</tr>
<tr>
<td>Tramadol (50 mg every four hours as needed)</td>
<td>Pain</td>
<td>Yes</td>
<td>Not used regularly.</td>
</tr>
<tr>
<td>Multivitamin (1 tablet daily)</td>
<td>Supplement</td>
<td>No</td>
<td>This was started because the patient had weight loss and poor intake of food and fluid. The nutritional support could potentially help.</td>
</tr>
</tbody>
</table>

Source: Compiled by Author

Table 4
As discussed, the reduction or discontinuation of medications should be done cautiously, generally one medication at a time. The provider reviews the drugs the patient usually takes, evaluating for polypharmacy or any prescribing problems with the drugs ordered (Table 4).

When reconciling the medication regimen, the first step is to identify the clinical indication for each medication. There are no obvious inappropriate prescribing practices in Patient T's record, and in a patient with multiple comorbidities, polypharmacy may become the standard. However, attempts at medication reduction and discontinuation should be attempted.

His primary care provider discusses the medication regimen with the patient and his daughter, who is his healthcare surrogate. They express interest in attempting to reduce the number of medications Patient T is taking.

The provider discontinues tramadol and writes orders to taper off omeprazole by giving every other day for 10 days, then stopping. The aspirin dose is reduced to 81 mg every day, and the atorvastatin is reduced to 10 mg daily with a plan for serial lipid measurements.

The ongoing dosages of furosemide and potassium are determined by the level of heart failure. When patients decline and lose weight, adjustments to diuretic dosages are required to prevent subsequent dehydration. Older patients are at increased risk of falls and complications due to orthostatic hypotension, and if the patient is dehydrated, the effects are more profound and potentially dangerous. Measurement of orthostatic vital signs will help to determine the appropriate dosage of metoprolol, lisinopril, and even furosemide. After the reconciliation, omeprazole and tramadol are discontinued and the dosages of several drugs are reduced (Table 5).

Comments and Discussion: Mr. T's case shows an example of multiple comorbid conditions and polypharmacy. There are no obviously inappropriate drugs, and each medication has a clinical indication consistent with evidence-based medicine. This makes medication reduction and reconciliation difficult.

When medication regimens are adjusted, the patient should be monitored and re-evaluated regularly to detect any adverse reactions. In some cases, a trial dosage reduction or discontinuation of a medication, with close monitoring of the patient response, is necessary.

Medication reduction in the elderly should be done slowly and conservatively to prevent rebound effects. Manufacturer and FDA recommendations should be followed for tapering to reduce or discontinue medications. The provider must refer to packaging inserts and information.
PALLIATIVE APPROACH TO MEDICATION REDUCTION

Individuals with life-limiting illnesses may not be candidates for curative or restorative therapy. These patients benefit from palliative care, defined as "processes of care designed to prevent and treat physical, emotional, and spiritual suffering in order to enhance quality of life for patients with chronic, progressive illnesses" [13]. Medications in palliative care provide comfort and address symptoms that impede function or negatively affect quality of life; many of these medications appear on the Beers List. In the case of terminal pain and suffering, medications known to cause side effects in the elderly may be used if the benefits outweigh the drawbacks. Providing care and comfort to a patient at the end of life may only be possible with the use of drugs that would be potentially inappropriate in patients without life-limiting disease.

The goals of care usually change with age, as patients develop multiple illnesses, functional decline, and/or dependency. Goals should be determined by individual preferences and regularly reassessed by the treatment team. Although there is great diversity in individual preferences regarding interventions at the end of life, most patients do not want to suffer or experience pain during this stage.

Including multiple oral medications in palliative care plans at the end of life can be a burden to patients and caregivers. At the end of life, a patient’s oral intake usually decreases due to dysphagia and a decline in the desire for food and fluids, and taking pills, tablets, or capsules may be difficult. Alternative routes of administration should be considered for these patients. Injectable medications are generally avoided due to the pain associated with administration, unless an intravenous line is available. As end-of-life care tends to take place in nursing facilities or at home, IV access is usually not available. However, transdermal, sublingual, sprays/tablets, buccal films, nasal sprays, suppositories, and lozenges may be appropriate. In addition, all medications not necessary to provide care and comfort to the patient should be discontinued.

As with any patient, informed consent should be obtained prior to the initiation of any new treatments or medications for patients receiving palliative care. This education should include potential benefits and risks of the proposed treatment. The responsible party should have the opportunity to ask questions, get a second opinion if desired, then accept or refuse any treatment or drug regimen.

CONCLUSION

Polypharmacy in geriatrics is a serious problem that is expected to grow in scope as the population ages. Certain medications commonly used in the younger population may be considered inappropriate in the elderly, due to pharmacodynamics, pharmacokinetics, and/or drug-disease interactions. The Beers criteria may be used to identify potentially inappropriate prescribing practices for elderly patients.

Many elderly patients live in assisted living or nursing facilities, and these facilities are subject to regulatory scrutiny at the state and federal levels. Drugs prescribed in the presence of adverse reactions, in excessive duration, in excessive dose, duplication of therapy, and/ or without clinical indications are considered unnecessary by regulatory bodies.

Healthcare professionals should conduct comprehensive assessments of their elderly patients. Social, financial, and/ or functional issues may increase the risk for ADRs, non-adherence, and medication errors. Prescribing practices commonly used for adults may cause more harm than benefit in elderly individuals. It is important to create individualized treatment plans that effectively communicate the risk-benefit profile of any drug or treatment. A multidisciplinary approach is necessary to provide optimal care to elderly patients in all care settings.
Audience
This course is designed for all healthcare professionals, including nurses, physicians, 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 sleep disorder patients with low English literacy.

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

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

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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 physiological and/or psychological 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; 4; 5]. Additionally, sleep apnea and narcolepsy are known to be responsible for some of the 800 fatalities and 44,000 nonfatal injuries caused by drowsy driving in the United States each year, adding to the considerable burden that untreated sleep disorders place on the healthcare system [6]. Other sleep disorders, including those that are transient, contribute to the remainder of the 72,000 annual crashes caused by excessive sleepiness while driving.

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 [7]. 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 [5; 8; 9; 10]. In 2015 dollars, this translates to $25 billion and $92.2 billion, respectively, and these figures do not take into account population growth or today's increased healthcare costs.
A 2011 study found that annual workplace losses (including workplace accidents) due to insomnia and associated comorbidities totaled $91.7 billion per year [57]. 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 [57]. 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 [111].

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 [3; 11; 12; 13; 14]. 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 [12]. However, only 11% of individuals who reported sleep complaints underwent any subsequent diagnostic testing, indicating a gap in factual knowledge and appropriate clinical behaviors [12].

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

**What are characteristics of normal 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 [59]. 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” [58]. Biological “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 [59]. 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 [59; 64]. There are three chronotypes (identifiable using the Horne-Ostberg 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 [64; 65]. 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) [64]. 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” [66]. 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 biological processes (e.g., body temperature, hormone production) [60; 61; 64]. 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 [62; 63]. 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 [59]. 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 [59; 118]. 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 [118]. 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 [118]. 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 [118].

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 [119]. Circulating melatonin levels increase in the hours following sunset and drop significantly upon eye exposure to light. It is believed that this hormone supplements and reinforces the entraining effects of the light period [119]. Whereas the ganglion cells provide a light cue to the SCN, melatonin provides a darkness cue via receptors in and around the structure.

**SLEEP STAGES**

The sleep process consists of five stages of sleep, divided into two general categories: rapid eye movement (REM) sleep and non-REM sleep. Non-REM sleep consists of four distinct phases (or stages), each of which is defined by a set of unique electrophysiologic parameters, including electroencephalogram (EEG), electromyogram (EMG), eye movements, and respiration. 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.

**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. 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 [51; 52]. 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.

**Stage 2**

Most time is spent in stage 2 sleep during an adult’s normal night’s sleep. 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 [51; 52].
Stages 3 and 4
Muscle tone continues to decrease progressively through stages 3 and 4. 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 20% to 50% of brainwave activity, and during stage 4, it is in excess of 50% [51; 52]. 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. For example, men 20 to 29 years of age spend 21% of total sleep time in slow-wave sleep; this decreases to 8% by 50 years of age and to 2% by 70 years of age. In elderly individuals, almost no time is spent in stage 4 sleep and little time is spent in stage 3.

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. 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 4 or 5 sleep cycles, each about 90 minutes, occur in one night, each one progressing through the non-REM stages, followed by REM sleep. Slow-wave sleep is lessened and REM sleep becomes more predominant with each successive sleep cycle (Figure 1) [54].

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 [53]. 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) [55]. SOREMPs are also seen with other disorders, including Prader-Willi syndrome, Kleine-Levin syndrome, Parkinson disease, and periodic limb movement disorder (PLMD) [55].

OVERVIEW OF SLEEP DISORDERS

According to the American Academy of Sleep Medicine, approximately how many unique sleep disorders are there?

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 7 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 3 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 7 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 [24]. 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 (AHl) 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 AHl 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 [24]. 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 AHl 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 AHl should be considered inaccurate and should be repeated (in a sleep lab whenever possible) [24].

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 [37].

**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); psycho-physiological 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 physiological condition, unspecified (nonorganic insomnia, not otherwise specified [NOS]); physiological (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 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/pathological 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.
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Features</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychophysiological insomnia</td>
<td>Elevated levels of somatic and cognitive arousal, especially when trying to sleep</td>
<td>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)</td>
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<td></td>
<td>Learned sleep-preventing associations</td>
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<td></td>
<td>Excessive focus on sleep</td>
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<td></td>
<td>Excessive worry about sleep</td>
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</tr>
<tr>
<td>Idiopathic insomnia</td>
<td>Early onset (i.e., infancy)</td>
<td>Gradual inability to sleep beginning at a very young age with no discernible cause</td>
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<tr>
<td></td>
<td>Genetic or congenital alterations in sleep-induction/arousal systems in the brain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No genetic markers are known</td>
<td></td>
</tr>
<tr>
<td>Paradoxical insomnia</td>
<td>Individuals underestimate the amount of sleep actually obtained</td>
<td>Extreme subjective sleep disturbance without objective corroboration</td>
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<td></td>
<td>Complaint of wakefulness in spite of sleep studies showing normal amounts of sleep</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Altered sleep/wake system</td>
<td></td>
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<tr>
<td>Inadequate sleep hygiene</td>
<td>Frequent napping/irregular sleep schedule</td>
<td>Inability to initiate sleep</td>
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<td></td>
<td>Regular use of caffeine, alcohol, tobacco, or other drugs close to bedtime</td>
<td>Chronic sleep/wake difficulty</td>
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<td>Regularly engaging in mentally, physically, or emotionally stressful activity before bedtime</td>
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<tr>
<td></td>
<td>Using the bed for activities other than sleep or sex (e.g., reading, television, video games)</td>
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</tr>
<tr>
<td></td>
<td>Inappropriate pre-sleep and sleep environment (e.g., too hot, excessive light, too loud or quiet)</td>
<td></td>
</tr>
<tr>
<td>Behavioral insomnia of childhood (sleep-onset association type or limit-setting type)</td>
<td>Poor sleep training or limit setting by caretakers or parents</td>
<td>Child’s dependence on specific objects, settings, or stimulation for initiating or returning to sleep (sleep-onset association type)</td>
</tr>
<tr>
<td></td>
<td>Some children are a mixed type</td>
<td>Bedtime stalling or refusal (limit-setting type)</td>
</tr>
</tbody>
</table>

Source: [2] Table 1

**Diagnosis in Adults**

*For patients with chronic insomnia, which conditions can trigger arousal near bedtime?*

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 [86].

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 biological 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.

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 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 to healthy individuals [91]. The Epworth Sleepiness Scale has been found to be particularly effective for identifying cases of insomnia and less useful for diagnosing other sleep disorders [93]. 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 and 4 sleep [84; 91]. as noted, many persons with insomnia sleep better outside of their own bed, and overnight laboratory testing may not provide significant data. Polysomnographic results also vary considerably from night to night in these patients [91]. Polysomnography is recommended for elderly individuals, as they are more prone to having identifiable etiologies of insomnia.
Approximately 7 in 10 of 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 psychological 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 7 to 8 hours each night to sleep, and creating and maintaining a bedtime ritual. The optimum sleep time varies among individuals, but those with persistent excessive daytime sleepiness should sleep a minimum of 6 to 8 hours [55].

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**THE ICS-D-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:
| 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
| F. The sleep/wake difficulty is not better explained by another sleep disorder.

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Reports of difficulties initiating sleep, difficulties maintaining sleep, or waking up too early can be seen in all age groups. Resistance 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).

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.

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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 [55]. 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 [55; 56; 57].

- Large, heavy meals should be avoided late in the day, as should spicy, new, or exotic foods.

<table>
<thead>
<tr>
<th>Situation</th>
<th>Score*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting and reading</td>
<td>0 = No chance of dozing</td>
</tr>
<tr>
<td></td>
<td>1 = Slight chance of dozing</td>
</tr>
<tr>
<td></td>
<td>2 = Moderate chance of dozing</td>
</tr>
<tr>
<td></td>
<td>3 = High chance of dozing</td>
</tr>
<tr>
<td>Watching television</td>
<td>0 = No chance of dozing</td>
</tr>
<tr>
<td></td>
<td>1 = Slight chance of dozing</td>
</tr>
<tr>
<td></td>
<td>2 = Moderate chance of dozing</td>
</tr>
<tr>
<td></td>
<td>3 = High chance of dozing</td>
</tr>
<tr>
<td>Sitting inactive in a public place (e.g., a theater or a meeting)</td>
<td>0 = No chance of dozing</td>
</tr>
<tr>
<td></td>
<td>1 = Slight chance of dozing</td>
</tr>
<tr>
<td></td>
<td>2 = Moderate chance of dozing</td>
</tr>
<tr>
<td></td>
<td>3 = High chance of dozing</td>
</tr>
<tr>
<td>As a passenger in a car for an hour without a break</td>
<td>0 = No chance of dozing</td>
</tr>
<tr>
<td></td>
<td>1 = Slight chance of dozing</td>
</tr>
<tr>
<td></td>
<td>2 = Moderate chance of dozing</td>
</tr>
<tr>
<td></td>
<td>3 = High chance of dozing</td>
</tr>
<tr>
<td>Lying down to rest in the afternoon when circumstances permit</td>
<td>0 = No chance of dozing</td>
</tr>
<tr>
<td></td>
<td>1 = Slight chance of dozing</td>
</tr>
<tr>
<td></td>
<td>2 = Moderate chance of dozing</td>
</tr>
<tr>
<td></td>
<td>3 = High chance of dozing</td>
</tr>
<tr>
<td>Sitting and talking to someone</td>
<td>0 = No chance of dozing</td>
</tr>
<tr>
<td></td>
<td>1 = Slight chance of dozing</td>
</tr>
<tr>
<td></td>
<td>2 = Moderate chance of dozing</td>
</tr>
<tr>
<td></td>
<td>3 = High chance of dozing</td>
</tr>
<tr>
<td>Sitting quietly after a lunch without alcohol</td>
<td>0 = No chance of dozing</td>
</tr>
<tr>
<td></td>
<td>1 = Slight chance of dozing</td>
</tr>
<tr>
<td></td>
<td>2 = Moderate chance of dozing</td>
</tr>
<tr>
<td></td>
<td>3 = High chance of dozing</td>
</tr>
<tr>
<td>In a car, while stopped for a few minutes in traffic</td>
<td>0 = No chance of dozing</td>
</tr>
<tr>
<td></td>
<td>1 = Slight chance of dozing</td>
</tr>
<tr>
<td></td>
<td>2 = Moderate chance of dozing</td>
</tr>
<tr>
<td></td>
<td>3 = High chance of dozing</td>
</tr>
</tbody>
</table>

*A total score of 10 or more from the eight criteria reflects above normal daytime sleepiness and need for further evaluation.

Source: [90] Table 3
• 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 [55; 56]:

• 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 [84; 85]. 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 [86]. 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 [85; 86; 87; 88; 89]. Patients also tend to prefer CBT over pharmacologic options and other forms of psychotherapy [87; 89]. Relaxation techniques (e.g., biofeedback, breath counting/deep breathing, meditation, progressive relaxation) can be an effective adjunct to CBT [87]. 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 [87].
According to the University of Texas at Austin School of Nursing, cognitive-behavioral therapy is recommended for first-line treatment of primary insomnia in older adults. Research supports that it is moderately effective in the treatment of primary insomnia. (http://www.guideline.gov/content.aspx?id=48218. Last accessed December 18, 2015.)

**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.)

Sleep restriction is also a useful form of therapy [87]. 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 [109]. 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 [92]. 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 [92]. 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 [92]. 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 6 to 8 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 [88]. If used, the lowest effective dose is recommended to reduce the incidence of these effects [88]. 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 [48].

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 [125]. 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.

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 [109]. The following are best practice guidelines regarding the prescription and use of sedative-hypnotics [109, 126]:

- 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 (1 to 2 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 aids, 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 (0.2–0.3 mg per night) for short periods (three months or less) [127]. 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).

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 [128]. This product is also unregulated by the FDA. Daytime drowsiness and rare instances of liver toxicity have been observed in association with its use.

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 3 months [2; 84]. 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 [56; 84].

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 the 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

What nasopharyngeal abnormalities are typical in adults with chronic obstructive sleep apnea?

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; 15]. 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., 6 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 [16; 22].

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. The AASM Task Force has defined the following cut-points for obstructive sleep apnea [3]:

- Normal: Less than 5 AHI
- Mild: 5 to 15 AHI
- Moderate: 15 to 30 AHI
- Severe: More than 30 AHI

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 [15]. 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 [16]. The incidence of the disorder increases with age, and it is 2 to 3 times more common in men than in women [15; 16]. The estimated incidence among various age-groups is [15]:

- Children: 2% to 8% among both sexes
- 30 to 65 years of age: 9% of women, 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. 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 [16]. 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 [17]. 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 [16; 18; 19]. Other obesity-related conditions, including insulin resistance, generalized inflammation, hypothalamic corticotropin-releasing hormone neurons, and visceral adiposity, have been suggested as factors in the development of obstructive sleep apnea following excessive weight gain [20]. 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 [17].

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 to normal weight controls [25].

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 [16; 18; 21]. A decade-long Wisconsin study of 690 randomly selected participants (mean age: 46 years) found that a 10% weight gain yielded a 6-fold increase in the odds of developing moderate-to-severe sleep disordered breathing compared to individuals who maintained a steady weight [17]. 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 [16; 18; 21; 22].

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 [24]. 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 [24]:

- 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 [24]:

- 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 nonpathological 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 [24]. 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.

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 when polysomnography is not available for diagnostic testing. (http://www.guideline.gov/content.aspx?id=48429. Last accessed December 18, 2015.)

**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 neurological 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

**OR**

- 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 (PaCO₂ > 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 [24].

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 [123]. 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) [24; 25]. 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 [25].

The American College of Physicians recommends continuous positive airway pressure treatment as initial therapy for patients diagnosed with obstructive sleep apnea.

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

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 [26]. 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 [26]. 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 [26]. A 2012 clinical trial summary showed that 19% of patients in the CPAP study group developed hypertension, compared to 22% in the control group (dietary and sleep hygiene counseling), and 8% of patients using CPAP had a cardiovascular event, compared to 8% in the control [27]. 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.

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 [123]. 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.

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 [28]. However, oral appliances were less likely to be discontinued than CPAP. 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 [24; 28].
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 [123]. 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 [22]. 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 [17; 24]. 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, especially with a dietary component alone, other treatment strategies should be employed simultaneously [24]. 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 [24]. 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.

### Behavior Modification

<table>
<thead>
<tr>
<th>Site</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper airway</td>
<td>Tracheotomy</td>
</tr>
<tr>
<td>Nasal</td>
<td>Septoplasty, Functional rhinoplasty, Nasal valve surgery, Turbinate reduction, Nasal polypectomy, Endoscopic procedures</td>
</tr>
<tr>
<td>Oral, oropharyngeal, and nasopharyngeal</td>
<td>Uvulopalatopharyngoplasty and variations, Palatal advancement pharyngoplasty, Tonsillectomy and/or adenoidectomy, Excision of tori mandibularis, Palatal implants</td>
</tr>
<tr>
<td>Hypopharyngeal</td>
<td>Tongue reduction, Partial glossectomy, Radiofrequency ablation, Lingual tonsillectomy, Tongue advancement/stabilization, Genioglossus advancement, Hyoid suspension, Mandibular advancement, Tongue suspension</td>
</tr>
<tr>
<td>Laryngeal</td>
<td>Epiglottoplasty, Hyoid suspension</td>
</tr>
<tr>
<td>Global airway</td>
<td>Maxillomandibular advancement, Bariatric surgery</td>
</tr>
</tbody>
</table>

*Source: [24] Table 4*
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 [24].

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 [29]. Candidates should also be screened for comorbidities that would affect the outcome of surgery. This and individual anatomy will dictate which option is chosen. Obstructive sleep apnea patients who have gross anatomical 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 [24]. 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 [24].

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 [29]. 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) [24]. 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 [29].

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) [24]. 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.

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 [24]. 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 HYPSOMNOLENCENCE

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 8 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 2 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

When do sleep attacks associated with narcolepsy usually occur?

Narcolepsy is a primary disorder of the CNS characterized by recurring episodes (every 2 to 3 hours) of extreme sleepiness, sudden and irresistible sleep attacks, disturbed nighttime sleep, and memory problems resulting from sleep deficit [2; 30]. 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 pathological REM sleep phenomena, including cataplexy, sleep paralysis, and hypnagogic/hypnopompic hallucinations.

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; 30; 67]. 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; 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 [37]. 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 [32; 33; 34]. The episode lasts 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 [67].

Most narcoleptic patients experience sleep paralysis, or an inability to speak or move for one to several minutes (up to 1 hour rarely) while transitioning into and out of sleep (hypnagogic and hypnopompic, respectively) [2]. Like cataplexy, sleep paralysis is a pathological 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 [37]. 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 [32; 33; 34]. Sleep paralysis is typically accompanied by hallucinations.

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 [35; 36]. 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) [35]. 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) [36]. 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 [35].

**Epidemiology**

Narcolepsy is the second most common sleep-related disorder in the United States (after obstructive sleep apnea), affecting an estimated 1 in 1000 individuals or 315,000 Americans [30; 31]. Men and women are equally affected, but prevalence varies by race/ethnicity. For example, compared to 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 3000 Americans [37]. 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 [37]. 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 [39; 40; 41]. 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 [37]. 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 [37; 68].
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 [37]. 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) [37].

**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 [37]. 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 to healthy individuals [37].

According to the European Federation of Neurological Societies, a prerequisite before implementing a potentially lifelong treatment is to establish an accurate diagnosis of narcolepsy with or without cataplexy and to check for possible comorbidity. Following a complete interview, the patient should undergo an all-night polysomnography followed immediately by a multiple sleep latency test. (http://www.guideline.gov/content.aspx?id=34901. Last accessed December 18, 2015.)

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

Laboratory testing may include cerebrospinal fluid (CSF) hypocretin-1 levels, but the value of this test is debated [2; 49]. 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 [49]. 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 [68].

**Treatment**

Narcolepsy is incurable, and the loss of hypocretin in patients with cataplexy is believed to be irreversible [37]. 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; 43]. 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 [44]. 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 [43].

If a CNS stimulant is prescribed in order to combat the effects of excessive daytime sleepiness, the most common are various amphetamines and methylphenidate [37; 42]. 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 [45]. 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 [42]. 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 [43]. 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 [49].
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 [49]. 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 [42; 46]. 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 [47]. 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 [48]. There is a low prevalence of common side effects, including headache (13%), nervousness (8%), nausea (5%), and rhinitis, all of which are typically mild [43; 49]. 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 [48]. 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 [49]. 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 [43]. 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 [48]. The initial dose is 4.5 g/night in two equal doses [48]. The first dose is taken sitting upright in bed just before sleep, and 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 2-week intervals up to a maximum dose of 9 g/night [48; 49]. Patients usually begin to improve after the first few days, 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) [48].

Antidepressants are considered second-line agents for cataplexy and are also an effective treatment for sleep paralysis and HHEs [49]. The most potent anticyclic antidepressants are tricyclic antidepressants, especially clomipramine (10–75 mg). However, these agents have the disadvantage of anti-cholinergic side effects. SSRIIs have fewer side effects but are slightly less active [49]. 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) [49]. 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 [49].

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 [49].

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 [49]. 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 [37]. Daytime napping has been shown to improve alertness and shorten reaction times [37]. Regular exercise (20 minutes/day, 4 to 5 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.

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 [37]. 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.
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 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 http://www.narcolepsynetwork.org. The Narcolepsy Network offers meetings in several U.S. cities and hosts online support groups as well [50].

IDIOPATHIC HYPERSONMIA

Idiopathic hypersomnia is a rare disorder, affecting approximately 50 people per million population [69]. 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 [70]. 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 [69; 70]. 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

What polysomnography findings are indicative of idiopathic hypersomnia?

There are many medical conditions that can cause hyper- somnia, 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 [69]. On the other hand, multiple SOREMPs (2 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 [69; 70]. Only half of patients treated report any improvement of symptoms. Although sleep hygiene practices are usually not helpful for idiopathic hypersomnia patients, they should be discussed because there are virtually no risks or drawbacks [69]. Patients should be advised to avoid sedative drugs and alcohol.

OTHER HYPERSONMNIAS

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; 71]. 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, psychological 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 [71]. The prevalence is greater in individuals of Jewish descent compared to the overall population [72]. 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 [72]. 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 psychological symptoms, including eating behavior disorders (95%), hypersexuality and disinhibition (53%), and depressed mood (53%) [72].

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 [73]. 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 [72; 73]. 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, physiological, 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

What factors may precipitate 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].

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 typically occurs during what sleep stage(s)?

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 [94; 108]. 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 [94; 108].

It should be noted that sleep driving associated with z-drugs (e.g., zolpidem, zopiclone) and other psychiatric medications is unrelated to sleepwalking [107]. 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 stages 3 and 4 (slow-wave sleep), which is more common early in the night (during the first-third of sleep) [94]. 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; 94]. 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 [96]. 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; 94]. 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 3 times higher in men than in women [100].

Sleepwalking may occur in isolated cases, but there is a known genetic susceptibility and a familial pattern [2; 101]. 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 [95]. 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; 94]. Individuals who are predisposed to sleepwalking may become active sleepwalkers when priming factors exist and a precipitating factor triggers an episode [2; 101]. 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/psychopathological interactions) [2; 94; 101]. 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; 94; 95]. Medication-related sleepwalking may occur, most commonly in individuals with a complex medical and psychiatric history associated with multiple medications [101]. The 2012 study found a higher risk of frequent sleepwalking episodes (≥2 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) [95].

**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 [94; 108]:

- 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; 94]. 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.
Sleep Disorders

Treatment

There is no cure or specific treatment for sleepwalking [94; 96]. 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 determine possible triggers, though dedication to observation and journaling lessens and more omissions occur over time [105].

Again, there is no high-quality evidence to support any specific sleepwalking treatment [96; 97]. 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) [94; 96]. However, the usefulness of these medications is not certain [102; 103]. Care must be taken when prescribing tricyclic antidepressants, as they have many serious side effects (especially in children) and can exacerbate sleepwalking [106]. Benzodiazepines (e.g., clonazepam, diazepam) were initially prescribed for sleepwalking, with only limited benefit [102; 103].

Another key to treatment is the maintenance of a safe living environment. Patient/parent education should cover precautions to be taken, including [96; 106]:

- 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

The patient is kept awake for 30 minutes and then may return the night and 15 minutes before the usual sleepwalking time. One behavioral approach, anticipatory awakenings, can be effective in reducing sleepwalking episodes. This method requires parents or caretakers to wake the patient 3 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 [104; 106].

Hypnosis has been used as a low-cost, safe therapy for various parasomnias, including sleepwalking [96]. 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 1 to 6 office visits and continued with at-home self-hypnotic exercises [98]. A 5-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 [99]. 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” [99].

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; 75].
Restless legs syndrome, also known as Willis-Ekbom disease, is a neurological 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 [74]. 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]. Pathological 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 [75]. 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 [74; 79].

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; 75]. 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 [79]. 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 [75]. 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 10% of the adult U.S. population is affected by restless legs syndrome, and women are affected twice as often as men [2; 73; 82]. 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 [73]. 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; 74]. It is unclear if the prevalence among older adults differentiates symptoms indicative of idiopathic 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 [79].

Risk Factors

There is a strong heritable risk factor for restless legs syndrome [74]. One study found that more than 70% of pediatric patients with restless legs syndrome had at least one parent with the disorder [73]. 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 [73; 75].

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 [75].
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) [79]. 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) [82]. 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 [120; 121].

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]. 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 [79].

Treatment

Which medications may be used in the treatment of restless legs syndrome?

Anticonvulsants, dopamine agonists, tranquilizers, and opioid narcotics are used to manage symptoms of restless legs syndrome, and iron supplements are used when indicated [74; 75]. Dopamine agonists considered effective for restless legs syndrome management include pramipexole and ropinirole, but rotigotine is recommended for long-term therapy [80].

<table>
<thead>
<tr>
<th>Timing of Symptoms</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms</td>
<td>0 (never)</td>
</tr>
<tr>
<td>Symptoms less than daily or almost daily</td>
<td>0.5 (infrequent)</td>
</tr>
<tr>
<td>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.</td>
<td>1 (mild)</td>
</tr>
<tr>
<td>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.)</td>
<td>2 (moderate)</td>
</tr>
<tr>
<td>Afternoon, before 6 p.m. Symptoms may start in the afternoon and persist into the evening or night.</td>
<td>3 (severe)</td>
</tr>
<tr>
<td>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.</td>
<td>4 (very severe)</td>
</tr>
</tbody>
</table>

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 [48; 74]. Gabapentin enacarbil is on-label and is preferred over gabapentin for long-term treatment [48; 80]. 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, 2 to 3 hours before bedtime, but higher doses (up to 0.5 mg) are typically required in order to be effective [48]. 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%) [48]. There is no evidence that doses higher than 0.5 mg/day offer benefit [110].

The initial dose of ropinirole (immediate-release) is 0.25 mg taken 1 to 3 hours before bedtime; the dose may be increased to 0.5 mg after 2 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%) [48].

Higher doses of gabapentin (2000–2400 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) [48; 76]. The recommended initial dose for restless legs syndrome treatment (off-label) is 300 mg taken 2 hours before bedtime; the dose may be titrated every 2 weeks, until desired response is achieved, to a maximum dose of 1800 mg [48]. (Dosages of up to 3,600 mg have been tolerated in short-term studies but are not recommended.) A combination of lower-dose gabapentin (300–1000 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 [76].

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 [48; 80; 81]. The dosage is 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 to 600 mg [48]. 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%) [48]. Pooled analysis of long-term use of gabapentin and other antiepileptic drugs has validated concerns regarding suicidal ideation and behavior (0.43%) compared to placebo (0.24%) [48]. Human data regarding pancreatic cancer risk have yet to be compiled, although gabapentin is associated with pancreatic adenocarcinoma in rats [48; 81].

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 [77; 78]. 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 [77; 78]. Pregabalin is usually taken in divided doses, either 2 or 3 times a day [48]. Dizziness and somnolence are the most frequent adverse effects [77].
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 [74; 79; 82]. Supplementation with specific vitamins and minerals known to support the nervous system and improve blood circulation (e.g., vitamins B12, C, D, and E; glucoseamine; 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 [82]. 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 psychological stress and lessen the severity of symptoms [74]. Endorphin release, dopamine production, and increased blood flow to leg muscles are believed to mediate symptoms [82]. 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. 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 [82]. 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 [82]. Near-infrared light therapy has also successfully reduced restless legs syndrome symptom severity in small-scale studies [122].

There is a strong placebo effect in restless legs syndrome therapy [82]. A 2008 meta-analysis of 36 clinical trials found that one-third of patients had a significant improvement while receiving placebo medications [83]. 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 [83].

In 2014, the FDA cleared the first device to improve sleep quality in patients with restless legs syndrome [124]. 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 6 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 [112].

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 [113]. 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 [113]. 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 [114]. Interpreters who are professionally trained have covered aspects of ethics, impartiality, accuracy, and completeness [115]. They also are well-versed in interpreting both the overt and latent content of information without changing any meanings and without intersecting their own biases and opinions [115]. 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 [114].
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 [116]. 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 [116]. Instead, the interpreter should be regarded as part of a collaborative team, bringing to the table a specific set of skills and expertise [116]. 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 [114; 116; 117]. 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 [115].

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?” [115]. The practitioner should also always refer to the client/patient as “Mr./Mrs. D,” rather than “he” or “she” [116]. 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 [116]. 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 [114]. The practitioner also should be attuned to the age, gender, class, and/or ethnic differences between the client/patient and the interpreter [116]. 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 [114; 116; 117].

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.
Colorectal Cancer

Includes 5 Pharmacotherapeutic/Pharmacology Hours

Audience
This course is designed for nurses, physicians, physician assistants, and other healthcare providers who may improve the identification and care of patients with colorectal cancer.

Course Objective
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.

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

1. Discuss the epidemiology of colorectal cancer.
2. Identify modifiable colorectal cancer risk factors.
3. Describe nonmodifiable risk factors, including familial and genetic colorectal cancer syndromes.
4. Evaluate the role of colonoscopy in colorectal cancer screening, including strategies to improve effectiveness.
5. Identify available modalities used in colorectal cancer screening.
6. Apply the correct colorectal cancer screening interval for patients with specific findings.
7. Describe the pathways by which colorectal cancer develops.
8. Discuss the histologic features of colorectal cancer precursor lesions.
9. Relate the diagnostic and staging criteria for colon and rectal cancers.
10. Identify molecular and clinical factors used to determine prognosis in patients with colorectal cancer.
11. Select the appropriate treatment approach for early stage (I–III) colon cancer.
12. Choose the most effective treatment option for patients with rectal cancer.
13. Analyze the role of chemotherapy in the treatment of colorectal cancer, including the action of specific agents.
14. Discuss the treatment of metastatic and recurrent colorectal cancers.
15. Describe potential treatment-induced toxicities and adverse effects in patients with colorectal cancer.
16. Outline recommended follow-up for patients treated for colorectal cancer.

Faculty
Mark Rose, BS, MA, is a licensed psychologist and researcher in the field of alcoholism and drug addiction based in Minnesota. He has written or contributed to the authorship of numerous papers on addiction and other medical disorders 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 various law firms on matters related to substance abuse, 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, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Division Planner Disclosure
The division planner has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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This course represents an educational model that promotes the importance of learning objectives and individualized learning. Study questions will appear throughout the course to create a link between the learning objectives and the supporting text.

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
Colorectal cancer is the second leading cause of cancer death in the United States, and roughly 50% of those who develop colorectal cancer die from the disease [1; 2; 3]. Improved therapies and widespread primary prevention through screening have resulted in the United States being the only developed country with declining colorectal cancer incidence and mortality [4]. However, there is substantial room for improvement, and primary care provider knowledge of colorectal cancer is essential to continue reducing cases through screening and early detection. While this course addresses important content domains related to colorectal cancer, a few related areas are not addressed: management of cancer-related pain and cancer of the anus. With 90% of anal cancer cases associated with the human papillomavirus (HPV), this malignancy is considered distinct from rectal cancer [5]. In contrast, rectal cancer bears such similarity to colon cancer that both cancers are frequently combined in epidemiological and clinical reports.

EPIDEMIOLOGY
In the United States, which racial group has the greatest colorectal cancer incidence and mortality?
Worldwide, colorectal cancer is the second most common cancer in women and the third most common in men [6]. The incidence varies geographically as much as 10-fold, with the highest estimated rates per 100,000 population in Australia/New Zealand (44.8 in men, 32.2 in women) and lowest in Western Africa (4.5 in men, 3.8 in women). The mortality rates per 100,000 have somewhat less variability, with the highest estimated mortality rates in Central and Eastern Europe (20.3 for men, 11.7 for women) and the lowest in Western Africa (3.5 for men, 3.0 for women) [6].

In the United States, colorectal cancer is the second leading cause of cancer death, with 134,490 new diagnoses and 49,190 deaths projected for 2016 [7]. From 2006 to 2010, colorectal cancer incidence rates declined by 3.7% per year in adults 50 years of age and older, but increased by about 1.8% per year in adults younger than 50 years of age. The survival rate has been increasing in both men and women for the past 20 years, and in 2011, an estimated 1.16 million persons were living with colon or rectal cancer in the United States [8; 9; 10].
Trends in the United States suggest a disproportionally higher incidence and death from colorectal cancer in black/African American patients than in white patients. Asian/Pacific Islander individuals have the lowest incidence and mortality from colorectal cancer [11]. The incidence of colorectal cancer is higher in men than in women, with the annual rate in men ranging from 39 per 100,000 for Asian/Pacific Islanders to 60.3 per 100,000 for African Americans. The annual incidence rate in women ranges from 29.2 per 100,000 in Asians/Pacific Islanders to 44.1 per 100,000 in African Americans. The annual age-adjusted mortality rates for men and women are 19.6 and 13.9 per 100,000, respectively.

The risk of colorectal cancer increases after 40 years of age and rises sharply at 50 to 55 years of age, with colorectal cancer risk doubling in every succeeding decade. Most cases of colorectal cancer are diagnosed after 50 years of age; only 4% are diagnosed in persons younger than 50 years of age [1; 9; 12].

Figures for rectal cancer alone are more difficult to ascertain because epidemiological studies usually report colon and rectal cancer together as colorectal cancer. However, 2016 projections estimate 39,220 new rectal cancer diagnoses [7].

Approximately 4.7% of Americans will be diagnosed with colorectal cancer at some point in their lifetime. Of those diagnosed, 50% will die from the disease. The overall five-year survival rate is 65%. Cancer stage at diagnosis strongly influences duration of survival. With colon and rectum cancer, the five-year survival is 89.8% in patients diagnosed with localized cancer, 70.5% with limited regional extension, and 12.9% with distant metastases [10]. Despite advances in surgical techniques and adjuvant therapy, the modest survival improvements in patients with advanced neoplasm provide the rationale for implementing primary and secondary preventive approaches to reduce morbidity and mortality from colorectal cancer [1; 2; 3].

**COLORECTAL CANCER RISK FACTORS**

What is the dominant overall risk factor for colorectal cancer for most people?

For most people, the dominant risk factor for colorectal cancer is increasing age. As noted, risk increases dramatically after 50 years of age. Other nonmodifiable factors, such as family history of colorectal cancer, personal history of colorectal cancer or high-risk adenomas, genetic predisposition, and inflammatory bowel disease, also elevate the risk of colorectal cancer [13]. There are also modifiable factors that increase (or decrease) an individual’s risk of colorectal cancer, including alcohol use, cigarette smoking, diet, and physical activity.

**MODIFIABLE FACTORS**

Factors Associated with Increased Risk of Colorectal Cancer

**Excessive Alcohol Use**

Solid evidence indicates that excessive alcohol use is associated with increased risk of colorectal cancer. Analysis of pooled data found that alcohol consumption greater than 45 g/day was associated with a 41% increase in risk of colorectal cancer [14; 15]. The more pronounced association between current alcohol intake and larger adenomas suggests that alcohol may act during the promotional phase of the adenoma-carcinoma sequence [14; 15].

**Cigarette Smoking**

Cigarette smoking is associated with an increased risk of colorectal cancer incidence and mortality, significantly increased risk of small and large adenomas, adenoma recurrence following polypectomy, and a long cancer induction period (35 years minimum). Rates of colorectal cancer mortality are highest in current smokers, intermediate in former smokers, and lowest in nonsmokers. Increased risk was observed after 20 years of smoking in men and women. A 1997 estimate from U.S. data attributed 12% of all colorectal cancer deaths to smoking [16]. Current smoking (vs. never smoking) increases the risk of developing colorectal cancer by 18% [17; 18].

**Obesity**

Obesity, defined as a body mass index (BMI) ≥30, has been consistently associated with increased incidence and mortality from colorectal cancer, particularly in men. Compared with BMI <22, the risk of colorectal cancer increases with a BMI ≥28.5 by 60% in men and 30% in women. A BMI ≥30 increases the overall risk of colorectal cancer by 45%. The mechanism of increased vulnerability to colorectal cancer in obese patients is not known but may involve the elevated release and bioavailability of growth factors, insulin, and insulin-like growth factor 1. Heightened risk in obese patients appears to be mitigated by high levels of physical activity [19; 20].

BMI is associated with risk of colorectal adenomas and colorectal cancer, but few studies have accrued large enough sample sizes to allow stratified analyses. Evaluation of pooled data from 8,213 participants in seven prospective studies found higher BMI was significantly associated with most histologic characteristics of metachronous adenomas in men, but not in women. The researchers concluded that body mass may affect colorectal carcinogenesis at comparatively early stages, particularly in men [21].
A study of 11,598 survivors of incident primary colorectal cancer examined the effect of obesity on risk of developing a second obesity-associated cancer (e.g., postmenopausal breast, kidney, pancreas, esophageal adenocarcinoma, endometrium). Compared with colorectal cancer survivors of normal prediagnostic BMI, the risk of developing a second obesity-associated cancer was increased 39% in overweight patients and 47% in obese patients [23]. This compares to the risk for developing a first primary obesity-associated cancer, which was increased by 18% in overweight persons and 61% in obese persons. The authors state that colorectal cancer survivors who were overweight or obese before diagnosis had an increased risk of second obesity-associated cancers relative to normal-weight survivors. Elevated risk of developing a second cancer in colorectal cancer survivors is more likely the result of the increased prevalence of overweight and obesity rather than increased susceptibility [23].

Researchers have associated a common mutation in colorectal cancer with elevated risk of metabolic disease. APC is a tumor-suppressor gene that indirectly regulates cell proliferation by encoding a protein called beta-catenin. APC inactivation by mutation leads to loss of beta-catenin function, which results in unchecked cellular replication and other processes that drive progression to malignant phenotype. Activation of the Wnt signaling pathway, normally mediated by beta-catenin, also occurs. Beta-catenin-Wnt signaling is involved in glucose metabolism and metabolic diseases such as obesity and type 2 diabetes. Using a molecular pathological epidemiology database, researchers found that risk of beta-catenin-negative colorectal cancer was significantly higher with greater BMI and lower with increased physical activity level. Risk of beta-catenin-positive colorectal cancer was unrelated to BMI or physical activity level [22].

Factors Associated with a Decreased Risk of Colorectal Cancer

Polyp Removal
Removal of adenomatous polyps significantly reduces the risk of colorectal cancer. This will be discussed in detail later in this course.

Physical Activity
A sedentary lifestyle has been associated with an increased risk of colorectal cancer, although this finding has not been consistent. More consistent is the association between regular physical activity and a decreased incidence of colon but not rectal cancer, with an estimated 24% risk reduction [24; 25].

Diet Low in Fat and Meat
Colon cancer rates are high in populations with high total fat intakes and are lower in those consuming less fat [26]. On average, fat comprises 40% to 45% of total caloric intake in high-incidence Western countries; in low-risk populations, fat accounts for only 10% of dietary calories [27]. Several case-control studies have explored the association of colon cancer risk with meat or fat consumption as well as protein and energy intake [28]. Positive associations with meat consumption or fat intake have been found frequently but have not always achieved statistical significance [29]. One hypothesis is that heterocyclic amines formed when meat or fish are cooked at high temperatures may contribute to the increased risk of colorectal cancers associated with meat consumption observed in epidemiologic studies [30; 31].

Diet High in Fiber
Despite evidence from case-control studies of a protective effect, results from a large prospective study found no difference in the risk of colorectal cancer between women in the highest quintile group compared with the lowest quintile group with respect to dietary fiber, after adjusting for age, known risk factors, and total energy intake [32].

Diet High in Fruits and Vegetables
Overall, results from more rigorously designed randomized controlled trials have washed out findings of significant correlation in earlier studies that linked higher fruit and vegetable consumption with lower rates of colorectal cancer. Diets low in fat and meat and high in fiber, fruits, and vegetables started as an adult do not appear to reduce the risk of colorectal cancer by a clinically important degree [33].
Lifestyle and Diet Modification in Recurrence Risk Reduction

Cohort studies have demonstrated associations between specific diet or exercise regimens with improvements in disease-specific and/or overall survival in patients following treatment for colorectal cancer, but these results have not been replicated by prospective randomized trials. When verification by more rigorous studies is absent, cohort study data should be interpreted with caution, because numerous uncontrolled variables are present that may confound the observational findings [13].

Physical Activity

A meta-analysis of prospective cohort studies evaluating physical activity in patients found a 25% reduction in colorectal cancer-specific mortality associated with any amount of physical activity (vs. no activity) and a 30% reduction associated with a high amount of physical activity (vs. low amount). After colorectal cancer was diagnosed, a 26% reduction in colorectal cancer-specific mortality was associated with participation in any physical activity (vs. no activity), and a 35% reduction associated with a high amount of physical activity (vs. a low amount) [34].

Diet

Among the observational study findings, patients with stage III colon cancer who had the lowest Western dietary pattern post-treatment showed significantly greater rates of disease-free survival and overall survival versus patients with highest Western dietary pattern [35; 36]. Also, patients with highest dietary glycemic load showed significantly greater overall survival rates compared with those with the lowest dietary glycemic load. Another uncontrolled cohort study of patients diagnosed with colorectal cancer found the extent of red and processed meat ingestion was associated with a 29% greater risk of death before colorectal cancer diagnosis, but red meat ingestion after diagnosis had no effect on overall mortality [37].

Plasma Vitamin D Level

There is evidence that vitamin D may be an important cofactor in immune protection against colorectal cancer risk. A large, population-based case-control study, derived from the Nurses’ Health Study and Health Professionals Follow-Up Study, found a significant association between plasma vitamin D level and colorectal cancer risk according to the degree of local antitumor immune response. The study consisted of 318 colorectal cancer cases and 624 matched controls. Subjects were divided into three groups based on the median plasma vitamin D level (tertile I 19.0 ng/mL, tertile III 37.4 ng/mL) and analyzed according to the degree of lymphocytic immune reactivity within and surrounding the tumor. Subjects in the highest vitamin D tertile were seen to have a significantly lower risk of developing colorectal cancer subtype showing an intense intratumoral cellular immune reaction. This association was not found for tumor subtypes characterized by a poor intratumoral immune response. The authors discuss possible mechanisms and conclude that these observations support a role for vitamin D in cancer immunoprevention through tumor-host interaction [38].

Chemoprevention

Chemopreventive agents are often prescribed to healthy subjects at risk for colorectal cancer, who will take the agent for the rest of their lives to prevent a potential cancer. In addition to the preventive benefit, this raises the bar very high when defining acceptable safety and toxicity [39]. Practice guidelines and expert opinion have been hesitant to recommend chemoprevention of colorectal cancer. One reason is that very promising earlier findings have often washed out under rigorous evaluation. Epidemiologic and large cohort studies have found a number of agents with significant association to reduced colorectal cancer risk. Not infrequently, these findings were verified by other observational studies, followed by identification in pre-clinical research of plausible mechanisms for a cause-effect relationship. However, then results from rigorous investigation using well-designed randomized controlled trials reveal new safety concerns or fail to confirm the significant relationships suggested by data from uncontrolled trials. Thus, guideline authors and experts are reluctant to suggest chemoprevention in the absence of large-scale, long-term, randomized controlled trials [40].

Use of surrogate endpoint markers in many chemoprevention trials may also dissuade recommendation. As the precursor of most colorectal cancers, adenomas have often been used as surrogate endpoints in efficacy evaluation of agents for prevention. Their use as surrogate markers of colorectal cancer in chemoprevention randomized controlled trials permits the reduction of the study observation period from roughly 10 years required for assessing colorectal cancer development to around 2 years. Despite the theoretical and pragmatic basis, preventive efficacy based on this surrogate endpoint may contribute to reluctance in recommending colorectal cancer chemoprevention [39].

The true benefit of chemoprevention is reliant on lifetime colorectal cancer risk in the patient population. Greatest potential benefit may come from use in patients diagnosed by colonoscopy with pre-malignant lesions, with family history of colorectal cancer, or genetically diagnosed and surgically resected for colorectal tumors. Chemoprevention will probably show modest benefit at best when used as prevention in average-risk patients [41; 42].
Cyclooxygenase Inhibitors

A 2015 prospective observational study published the first-ever results of cyclooxygenase-2 (COX-2) inhibitor and aspirin use as adjuvant therapy following resection in patients with stage III colon cancer. All patients received standard adjuvant chemotherapy with fluorouracil (5-FU) plus leucovorin with or without irinotecan. In the aspirin arm of 799 patients, 75 (9.4%) used aspirin during and after chemotherapy. In the COX-2 inhibitor arm of 843 patients, 59 (7.5%) used celecoxib or rofecoxib after completing chemotherapy. Both groups had a median follow-up of 6.5 years [43]. Among patients taking aspirin (vs. no aspirin), recurrence-free survival (i.e., time period until tumor recurrence, death with recurrence, or development of a new invasive colon cancer) was increased by 49%, disease-free survival (i.e., time period until tumor recurrence, occurrence of a new colon cancer, or death from any cause) was increased by 32%, and overall survival (i.e., time period until death from any cause) was increased by 37%. Adjusted hazard ratios were censored at five years to minimize misclassification from non-cancer death and showed increases in disease-free survival by 39% and overall survival by 52% (vs. no aspirin). Patients taking a COX-2 inhibitor (vs. no COX-2 inhibitor) found increases in recurrence-free survival by 47%, disease-free survival by 40%, and overall survival by 50%. Censor of survival data at five years found disease-free survival increased by 53% and overall survival by 74% [43].

Although this study was not designed to identify the optimal dose and duration of aspirin or COX-2 inhibitors for protection against colorectal cancer, the data suggest a dose-response relationship in aspirin with increased frequency, while any dose of COX-2 inhibitors was associated with benefit. The statistically significant associations between aspirin and COX-2 inhibitor use and reduced colon cancer recurrence and mortality found in this study will continue to be evaluated [43].

Celecoxib, rofecoxib, and aspirin share a similar mechanism of action in colon (and presumably rectal) cancer involving COX-2 inhibition. COX synthesizes the conversion of arachidonic acid to prostaglandins. Prostaglandins mediate tumor growth by altering stem cell gene expression, hyper-methylating genes involved in proliferation and differentiation, promoting angiogenesis and Wnt/CTNNB1 signaling, and inhibiting apoptosis. Thus, suppression of prostaglandin synthesis through COX inhibition interferes with the processes involved in tumor promotion and growth [43; 44].

Long-term follow-up data from two large studies initiated in the 1980s found that ≥300 mg aspirin daily taken for five or more years was associated with a 37% overall reduction in colorectal cancer risk. In subjects who remained adherent to the protocol for 5 or more years, those randomized to aspirin were found to have a 40% risk reduction in colorectal cancer mortality after 20 years and absolute risk reduction from 3.1% to 1.9% relative to those receiving placebo. Mortality reduction was primarily from the effect of aspirin on proximal colon cancer. These findings were serendipitous, because the research was designed to examine the protective effects of aspirin against cardiovascular events [45; 46].

Prospective studies have demonstrated significant reduction in colorectal cancer among regular aspirin users [47]. In a randomized controlled trial of 861 persons with Lynch syndrome, primary colorectal cancer developed in 4.2% of patients taking daily aspirin 600 mg, compared with 6.9% in those receiving daily placebo (mean follow-up: 55.7 months). Time to first colorectal cancer was increased 37% with aspirin versus placebo; with regression analysis incorporating multiple primary events, aspirin led to a 44% reduction in colorectal cancer incidence. In subjects completing at least two years of intervention, time to first colorectal cancer was increased 59% and incidence of colorectal cancer was reduced 63%. Adverse events did not differ between aspirin and placebo groups during the intervention [48]. Likewise, a randomized controlled trial of patients with a history of adenomas or colorectal cancer found a statistically significant 21% reduction in risk of adenoma recurrence in patients randomized to aspirin (versus placebo) [49].

A prospective cohort study examined the effects of aspirin in participants following a diagnosis of colorectal cancer. Regular use of aspirin after colorectal cancer diagnosis was associated with a 29% increase in colorectal cancer-specific survival and a 21% increase in overall survival [50]. In the long-term Nurses’ Health Study and the Health Professional Follow-up Study, 964 patients diagnosed with rectal or colon cancers were evaluated. In those with PI3K-mutant colorectal cancer, regular use of aspirin was associated with a 46% increase in overall survival [51].

Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with potentially serious adverse effects that should be considered when determining the risk-benefit ratio [49]. Aspirin use can result in excessive bleeding, gastrointestinal bleeds, and hemorrhagic stroke. The estimated average increased risk of upper gastrointestinal complications was 10 to 30 per 1,000 people over a 10-year period, with men on the higher end and women on the lower end. Risk increases with age [52].
While no studies have assessed adenoma or colorectal cancer risk reduction with use of NSAIDs in the general (and presumably average-risk) population, multiple lines of evidence from epidemiologic studies, observational cohort studies, and randomized controlled trials have consistently affirmed the association between NSAID use and a 30% to 50% reduction in adenomatous polyps, incident disease, and death from colorectal cancer [49; 53; 54; 55]. In one study, patients with familial adenomatous polyposis (FAP) who were followed over four years of treatment with NSAIDs showed a trend in reduction in adenoma incidence and statistically significant reductions in polyp number and size. A 34% reduction in adenoma recurrence risk and a 55% reduction in advanced adenoma incidence were found in patients with a history of adenomas [49].

The NSAIDs sulindac and celecoxib have been shown in randomized controlled trials to induce adenoma regression in patients with FAP, which, together with supportive preclinical data, led the U.S. Food and Drug Administration (FDA) to approve celecoxib for patients with FAP in 1999. However, in 2011, the FDA requested Pfizer voluntarily withdraw the FAP indication for celecoxib, because the company never fulfilled a condition for approval requiring postmarketing evaluation to verify clinical benefit, which Pfizer did [56]. Despite the change of celecoxib use in off-label status and withdrawal of regulatory approval, several health insurance companies have codified the use of celecoxib in FAP as an authorized indication [57].

The consistently positive findings of NSAID benefit in suppressing the development of adenomas and improving recurrence-free, disease-free, and overall survival in patients with histories of adenomas and colon cancer has posed a dilemma for researchers and clinicians, given the known toxicity profile. NSAID-related morbidity is fairly common and potentially serious and includes upper gastrointestinal bleeding, renal dysfunction, and serious cardiovascular events such as myocardial infarction, heart failure, and hemorrhagic stroke. Among other findings, use of NSAIDs increases the risk of serious cardiovascular events by 50% to 60% [53; 58].

Hormones (for Women Only)
The Women’s Health Initiative (WHI) randomized participants to estrogen plus progestin or placebo. At a mean follow-up of 11.6 years, women receiving active hormone therapy had a 28% lower risk of colorectal cancers [59]. However, in the hormone therapy group, colorectal cancers that developed were significantly more likely to exhibit lymph node involvement and higher stages (regional and distant) compared with those in the placebo group. Deaths from colorectal cancers in the active group were somewhat higher, but the difference from placebo was not statistically significant [59]. A meta-analysis of cohort studies observed a 14% risk reduction for incidence of colorectal cancer associated with combined hormone therapy [60].

Conjugated equine estrogens do not improve incidence or survival in invasive colorectal cancer [59]. Definite harms have been established in using combined estrogen plus progestin hormone in postmenopausal women. The WHI trial found increased risks of invasive breast cancer, coronary heart disease events, and thromboembolic events [59; 61].

Vitamin Supplementation

Vitamin E
A prospective cohort study of 35,215 women found an inverse association between the risk of colon cancer and vitamin E intake [62]. However, a later cohort study found no relationship between every-other-day use of vitamin E 600 IU and colorectal cancer, and a meta-analysis of 14 randomized trials of supplemental antioxidant vitamins involving 170,025 individuals found no evidence for prevention of colorectal adenoma or colorectal cancer [63; 64].

Vitamin D
A systematic review of published cohort studies found that daily intake of 1,000 IU of vitamin D and 25-hydroxyvitamin D serum concentration of 33 ng/mL were each associated with a 50% risk reduction of colorectal cancer [65]. A population-based case-control study found an inverse relationship between vitamin D intake and colorectal cancer risk [66].

Folate
An observational study of women with a family history of colon cancer found use of folic acid supplements for more than 15 years was associated with a 75% lower risk of colorectal cancer [67]. One hypothesis is that folate is required for DNA synthesis, and suboptimal amounts may cause abnormalities in DNA synthesis or repair [68]. However, a trial that randomized 1,021 men and women with recent colorectal adenoma or colorectal cancer history to daily folic acid 1 mg or placebo found folic acid was associated with greater risks of developing ≥1 advanced adenoma, ≥3 adenomas, and extra-colonic malignancy compared with placebo [69]. General population studies have not found benefit of folic acid on colorectal cancer risk, but outcomes obtained over relatively short duration may have missed detection of benefit from longer exposure and/or follow-up [49].
Calcium
Researchers have suggested that calcium’s action of binding bile acids and fatty acids may lower colon cancer risks through reducing exposure to toxic intraluminal compounds [70]. To study the effects of calcium on adenoma recurrence, persons with a recent history of colorectal adenomas were randomized to daily 3 g calcium carbonate (1,200 mg elemental calcium) or placebo. At four-year follow-up, those receiving calcium (compared with placebo) showed a 19% reduction in developing ≥1 recurrent adenoma and the average number of adenomas was 24% lower. This reduced risk was likely to extend up to five years following cessation of calcium supplementation [71; 72].

Calcium has not shown benefit in patients with FAP. In the general population, there was no significant effect of calcium on risk of colorectal cancer, although studies were of relatively short duration [49]. There is fair evidence that 1,000–1,200 mg/day oral calcium without vitamin D supplementation increases the risk of myocardial infarction. Calcium supplementation with vitamin D at doses less than 1,000 mg/day has few harmful effects [73; 74].

NOMODIFIABLE RISK FACTORS
While most cases of colorectal cancer result from complex interactions between inherited susceptibility and environmental or lifestyle factors, certain heritability factors place the individual at very high risk of colorectal cancer, while other patterns of familial colorectal cancer elevate individual risk. Furthermore, specific medical conditions are associated with colorectal cancer risk. The presence or absence of these nonmodifiable risk factors influences the probability that colorectal cancer will develop. Assessment and identification of these risk factors determines the timing, frequency, and modality of colorectal cancer screening and intervention [75; 76].

Assessment of Nonmodifiable Colorectal Cancer Risk Factors
Clinicians should perform an individualized assessment of colorectal cancer risk in all adults in order to understand patient risk level for colorectal cancer. Patient risk is assessed by a thorough personal and family history to identify factors associated with increased vulnerability to colorectal cancer. The colorectal cancer risk factors of smoking, obesity, coronary artery disease, diabetes, acromegaly, renal transplantation, and cholecystectomy have no bearing on the timing, frequency, and modality of colorectal cancer screening or intervention (in the absence of adenomatous polyps or colorectal cancer) [77].

Familial Colorectal Cancer Risk Factors
A targeted colorectal cancer family history should include a detailed family history of cancer and polyps, especially in first-degree (e.g., parent, sibling, child) and second-degree (e.g., grandparent, uncle/aunt, half sibling) relatives on both sides of the family [78]. Clinicians should ask about polyps in relatives, including:

- Age at first colon exam
- How diagnosed (e.g., colonoscopy, flexible sigmoidoscopy, barium enema)
- How many (during each colonoscopy or lifetime total)
- Type (adenomas, hyperplastic, juvenile, serrated, hamartomas)
- Polyp surgery
- Diagnoses:
  - Colorectal cancer (and age at diagnosis)
  - Polyposis syndrome
  - Extracolonic conditions such as osteoma, sebaceous cysts, desmoid tumors, congenital hypertrophy of retinal pigment epithelium (CHRPE), or extra teeth
- Genetic testing for polyposis or hereditary cancer
- Is relative willing to sign release to share relevant medical records?

In addition to familial factors, patients’ personal risk factors should also be assessed (Table 1).

Patients should be assessed for all cancer types. Cancer syndromes include risk for multiple types of malignancy; colorectal cancer is not always a presenting cancer. A three-generation pedigree is the gold standard. The minimum for colorectal cancer should include cancer and polyp history for the patient’s generation and two previous generations. The patient’s risk status can change over time with updated personal or family history.

Assessment Red Flags
Findings suggestive of heritable colorectal cancer risk are termed “red flags” and direct the healthcare provider to probe further. One red flag is a personal history of colon cancer diagnosed before 60 years of age or endometrial cancer diagnosed before 50 years of age [78]. Early age at diagnosis suggests that genetic factors are playing a strong role in the development of disease.
A family history of colon or endometrial cancer diagnosed before 50 years of age is another red flag. Early age at diagnosis of cancer in a closely related family member suggests that genetic factors are playing a role in the development of disease, and these factors can be passed on to other relatives. If multiple family members have been diagnosed with colorectal cancer, or other Lynch/hereditary nonpolyposis colorectal cancer (HNPCC)-related cancers, this strongly suggests genetic factors are increasing individual cancer risks, especially among first-degree relatives.

One to two polyps in a lifetime is common, but more than 10 in a lifetime is unusual and suggests genetic contribution. Polyposis is associated with increased colorectal cancer risk. In addition, diagnosis of two or more Lynch/HNPCC-associated cancers suggests an inherited mutation, increasing the overall risk for cancer in different organs.

Past diagnosis of Lynch/HNPCC, FAP, or other inherited cancer syndrome in a family member is another risk factor. Many of these conditions are inherited in a dominant pattern, but not everyone who inherits gene mutations for these conditions develops cancer. Therefore, a diagnosis of HNPCC in a grandparent may be relevant to the patient.

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**Patient Colorectal Cancer Risk Level**

**What factors place a patient at high risk for colorectal cancer?**

Of total colorectal cancer cases, 75% are due to sporadic disease without apparent inherited origin, 10% to 30% are due to familial risk factors, and 5% to 6% are due to heritable genetic mutations. The absolute risk of colorectal cancer by 79 years of age is [79; 80]:

- 4% with no family history
- 9% with colorectal cancer in one first-degree relative
- 16% with colorectal cancer in two or more first-degree relatives
- 15% with colorectal cancer in one first-degree relative diagnosed before 45 years of age
- 8% with colorectal adenoma in one first-degree relative

Family history of two or more relatives with colorectal cancer substantially increases the possibility of a genetic syndrome, and relative to older individuals, young patients reporting a positive colorectal cancer family history are more likely to represent a high-risk pedigree [81; 82]. Patient risk level is categorized as high, increased (moderate), or average based on the presence of specific factors (Table 2) [78].
Familial and Genetic Colorectal Cancer Syndromes

Heritable gene mutations that confer elevated risk of colorectal cancer broadly cluster into two groups: stability genes, including mutations in DNA mismatch repair (MMR) genes responsible for Lynch syndrome, and tumor suppressor genes, including APC gene mutations responsible for FAP. Lynch syndrome and FAP account for the vast majority of heritable colorectal cancer cases and 5% to 6% of all colorectal cancer cases [78]. The absolute risks for colorectal cancer in mutation carriers of hereditary colorectal cancer syndromes are [78]:

- **Lynch syndrome**: 24% to 75% by 75 years of age
- **FAP**: Nearly 100% by 45 years of age
- **Attenuated FAP**: 70% lifetime
- **MYH-associated polyposis**: Nearly 100% by 65 years of age
- **Peutz-Jeghers syndrome**: 39% by 70 years of age
- **Juvenile polyposis syndrome**: 17% to 68% by 60 years of age

Individuals with single-gene disorders are at increased risk of developing colorectal cancer, and single-gene disorders related to known syndromes account for 10% to 15% of colorectal cancer cases. The hereditary syndromes and involved genes include Lynch syndrome, FAP, familial colorectal cancer, and rare genetic syndromes [78].

Lynch Syndrome

Lynch syndrome is the most prevalent form of hereditary colorectal cancer, accounting for 3% to 5% of all cases. It primarily involves defects in MMR genes, most commonly MSH2, MLH1, PMS1, PMS2, or MSH6. In affected families, 15% to 60% of family members possess MSH2 or MLH1 mutations [79; 83].

Lynch syndrome is an autosomal dominant disorder in which families and patients possess a germline mutation in a DNA MMR gene or loss of expression of the MSH2 gene due to deletion in the EPCAM gene. These genes function to maintain DNA fidelity during replication and are inactivated in Lynch syndrome [84].

Genetic Testing. Genetic risk assessment of Lynch syndrome considers family cancer history and patient age if diagnosed with colorectal cancer or malignancies associated with Lynch syndrome. Mutation in MMR genes can be detected using immunohistochemistry techniques (IHCs) or DNA microsatellite instability (MSI) analysis. Several validated computer models predict MMR gene mutation probability (even when MSI or IHC information is absent) and also incorporate family history of endometrial cancer. Mutation detection rates are higher for patients with more striking family histories or informative tumor testing data [85; 86].

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### COLORECTAL CANCER RISK LEVELS

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Factors</th>
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<tbody>
<tr>
<td>Average</td>
<td>Lack of specific risk factors</td>
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</tbody>
</table>
| Increased (moderate)| Inflammatory bowel disease  
Previous colonoscopy polyp findings:  
- Small rectal hyperplastic polyps  
- 1–2 small tubular adenomas with low-grade dysplasia  
- 3–10 adenomas  
- 1 adenoma >1 cm  
- Any adenoma with villous features or high-grade dysplasia  
- >10 adenomas on a single examination  
- Sessile adenomas removed piecemeal  
Family history:  
- Colorectal cancer or adenomatous polyps in a first-degree relative  
- Two second-degree relatives with colorectal cancer |
| High                | Diagnosis of Lynch/HNPCC or FAP  
Family or medical history highly suggestive of hereditary colorectal cancer syndrome |

*Source: [78] Table 2*
Clinical Features. Colorectal cancer and extracolonic malignancies are the primary consequences of Lynch syndrome. Colorectal cancer associated with Lynch syndrome is characterized by early age of onset, excess synchronous and metachronous colorectal neoplasm, right-sided dominance (roughly 67%), and extracolonic tumors. The average age of colorectal cancer diagnosis in patients with Lynch syndrome is 44 to 52 years, versus 71 years in sporadic colorectal cancer. MLH1 and MSH2 account for close to 90% of gene mutations, and the lifetime risk of colorectal cancer in MLH1 and MSH2 mutation carriers is 68.7% in men and 52% in women [84].

Risk of extracolonic malignancy is greatest for endometrial cancer. At least one female member in about half of all Lynch syndrome pedigrees is affected, and 50% of women with an MMR gene mutation present with endometrial cancer as first malignancy. Patients with Lynch syndrome have an elevated risk of several other cancers. Risk of extracolonic tumor development by 70 years of age in Lynch syndrome is shown below, with prevalence rate ranges reflecting differences between specific MMR mutations [84]:

- Endometrial (MLH1/MSH2): 14% to 54%
- Ovarian: 4% to 20%
- Urinary tract: 0.2% to 25%
- Stomach: 0.2% to 13%
- Small bowel: 0.4% to 12%
- Brain/central nervous system: 1% to 4%
- Prostate: 9% to 30%
- Breast: 5% to 18%

The adenoma-carcinoma sequence of polyp-to-cancer dwell time is an estimated mean 35 months, considerably more rapid than the 10- to 15-year average in sporadic colorectal cancer. This accelerated rate is likely the result of MMR gene dysfunction that creates frequent DNA mismatches in multiple genes to disrupt their normal function [84]. Until recently, Lynch syndrome was termed hereditary nonpolyposis colorectal cancer, a misnomer because polyps are usually present [87].

Diagnosis. Clinical criteria to identify patients with Lynch syndrome were published in 1990 and termed the Amsterdam criteria. These were revised and expanded with the 1999 Amsterdam II criteria, which included extracolonic cancers. The Amsterdam II defines minimum criteria for a clinical diagnosis of Lynch syndrome as at least three relatives with a Lynch-associated cancer (e.g., colorectal cancer, endometrial, small bowel, ureter, renal pelvis) and [88]:

- Two or more successive generations affected
- One or more relatives diagnosed before 50 years of age (at least one first-degree relative)
- FAP excluded
- Tumors verified by pathologic examination

The 2004 updated Bethesda Guidelines were developed to improve the false-negative rates with Amsterdam II and outline criteria to prompt MSI tumor testing to identify Lynch syndrome. Tumors meeting one or more of these criteria require testing for MSI [89]:

- Colorectal cancer diagnosed at 50 years of age or younger
- Synchronous or metachronous Lynch-associated cancer present, regardless of age
- Colorectal cancer with Lynch-like histology (e.g., tumor infiltrating lymphocytes, Crohn-like lymphocytic reaction, mucinous/signet-ring differentiation, medullary growth pattern) in patients younger than 60 years of age
- Colorectal cancer in a patient with one or more first-degree relatives with Lynch-associated cancer diagnosed at or before 50 years of age
- Colorectal cancer in a patient with two or more first- or second-degree relatives with a Lynch-associated tumor, regardless of age

Although more sensitive than Amsterdam II in identifying families with Lynch syndrome, only 15% to 30% of families not meeting Amsterdam II but meeting Bethesda criteria exhibit MSI gene mutation. Thus, Amsterdam II or Bethesda criteria may be used to help identify patients who should receive genetic testing, but they should not be used as diagnostic instruments [90].
Surveillance. The differing surveillance approach in persons with Lynch syndrome relative to average-risk persons is dictated by the biologic behavior of Lynch syndrome [91]. Lynch syndrome develops earlier than sporadic colorectal cancer, which suggests screening should begin earlier in life. Most Lynch syndrome colorectal cancers occur in the right colon, making sigmoidoscopy alone insufficient. Annual colonoscopic surveillance is recommended. The accelerated progression from normal mucosa to adenoma to cancer suggests a shorter colonoscopy screening interval (i.e., every one to two years). The substantially higher lifetime incidence of colorectal cancer suggests that surveillance should use the most sensitive test available.

Patients with Lynch syndrome are at an elevated risk of extracolonic cancers, especially endometrial and ovarian. While routine screening in women with Lynch syndrome is recommended due to substantially increased risk of endometrial cancer, routine transvaginal ultrasound screening for endometrial cancer is insensitive, nonspecific, and without benefit in the general population.

Interventions. A study randomized 861 Lynch mutation carriers to daily aspirin 600 mg or placebo. No difference was found at 24 months, but 56-month follow-up found somewhat lower adenoma rate and colorectal cancer risk in the aspirin group. Further analysis found decreased incidence of all Lynch-associated cancers in the aspirin group [48]. Prophylactic surgery is an alternative to annual colorectal cancer and endometrial cancer screening. The high risk of developing metachronous lesions is the basis for prophylactic surgery [90]. The incidence of metachronous colorectal cancers has been reported to be 16% at 10 years, 41% at 20 years, and 63% at 30 years following segmental colectomy [92]. With the increased incidence of synchronous and metachronous neoplasms, the treatment of choice for a patient with Lynch syndrome with neoplastic lesions in the colon is generally an extended colectomy. The results of a follow-up study help in the selection of surgical approach. In this trial, 382 MMR mutation carriers were followed over time after surgery. During follow-up, metachronous colorectal cancer developed in no patient receiving total or subtotal colectomy compared with 22% of patients receiving segmental colectomy [93; 94]. An important factor in the decision to offer prophylactic surgery is the ability of the patient to comply with surveillance examinations.

Consideration of total or subtotal colectomy should be balanced with patient comorbidities, clinical stage of the disease, patient wishes, and surgical expertise. No data have been published showing a survival advantage in extended versus segmental resection for patients with Lynch syndrome. Also, subtotal or total colectomy does not eliminate rectal cancer risk, and the risk of developing rectal cancer following abdominal colectomy is estimated at 12% at 12 years post-surgery [92; 95].

Familial Adenomatous Polyposis

FAP accounts for 1% of all colorectal cancers and involves germline mutations in the tumor suppressor gene APC [79; 83]. Ashkenazi Jews have elevated risk of colorectal cancer due to APC gene mutation, which occurs in 6% to 7% of this population [96]. Other FAP disorder variants include [79; 83]:

- Attenuated FAP: APC gene
- Turcot syndrome: APC gene, MMR genes
- Hyperplastic polyposis syndrome: BRAF and KRAS2 genes
- MYH-associated polyposis: MYH gene

Genetic diagnosis of FAP in pre-symptomatic patients is performed with linkage or direct detection of APC mutations. FAP diagnosis is performed by analyzing lymphocyte DNA in a blood sample. Linkage analysis tests blood samples from multiple persons to identify gene carriers in close and ancillary family members [79; 83; 90].

Clinical Features. FAP is caused by parental transmission of mutation in the APC gene, a tumor suppressor or gatekeeper gene that controls cell proliferation. The most common FAP phenotype is development of hundreds to thousands of colorectal polyps, with usual onset during adolescence or early adulthood. Malignancy develops in one or more polyps as early as 20 years of age, and colorectal cancer develops in almost 100% of patients by 40 years of age if the colon is not removed for primary prevention. Other characteristics of FAP can include polyps in the upper gastrointestinal tract; extracolonic manifestations, such as congenital hypertrophy of retinal pigment epithelium, osteomas and epidermoid cysts, supernumerary teeth, and desmoid formation; and other malignancies, such as thyroid tumors, small bowel cancer, hepatoblastoma, and brain tumors (particularly medulloblastoma) [79; 83; 90]. The lifetime risk of extracolonic tumor development in FAP is [97]:

- Desmoid: 15%
- Duodenum: 5% to 12%
- Thyroid: 2%
- Brain: 2%
- Ampullary: 1.7%
- Pancreas: 1.7%
- Hepatoblastoma: 1.6%
- Gastric: 0.6%
**Diagnosis.** The clinical diagnostic criteria of FAP is a patient with 10 to 99 adenomatous colon polyps diagnosed by 40 years of age, or more than 100 polyps diagnosed at an older age than expected [91].

**Surveillance.** The recommended age at which surveillance for polyposis should begin involves a trade-off. On one hand, a patient who waits until the late teens to begin surveillance faces a remote possibility that a cancer will have developed at an earlier age. Although it is rare, colorectal cancer can develop in a teenager who carries an APC mutation. On the other hand, it is preferable to allow people at risk to develop emotionally before they are faced with a major surgical decision regarding the timing of colectomy. Therefore, surveillance is usually begun in the early teenage years (10 to 15 years of age). Surveillance has consisted of either flexible sigmoidoscopy or colonoscopy every year. If flexible sigmoidoscopy is utilized and polyps are found, colonoscopy should be performed. Historically, sigmoidoscopy may have been a reasonable approach at the time in identifying early adenomas in a majority of the patients [98]. However, colonoscopy should be considered the tool of choice in light of improved instrumentation for full colonoscopy, safer and deeper sedation (with propofol), recognition that malignancy is more common in the right colon with attenuated FAP, and the growing tendency to defer surgery for a number of years. Individuals testing negative for an otherwise known family mutation do not need FAP-oriented surveillance and can undergo average-risk population screening. In the case of families where no family mutation has been identified in an affected person, clinical surveillance is warranted [79; 83; 90].

Colon surveillance should not be stopped in carriers of an APC mutation who do not yet manifest polyps, because adenomas occasionally do not appear before the fourth and fifth decades of life. In some circumstances, full colonoscopy is preferred over the more limited sigmoidoscopy. Tolerance of endoscopic procedures among pediatric patients has improved with the use of deeper intravenous sedation [79; 83; 90].

**Interventions.** After an APC mutation is identified in a patient or member of their family, evaluation for polyposis by flexible sigmoidoscopy or colonoscopy begins promptly. In those showing polyps, the only effective management to prevent colorectal cancer is eventual colectomy. In patients with early-stage classic FAP, the surgeon, endoscopist, and patient/family may opt to delay surgery for several years in the interest of achieving social milestones. Carefully selected patients with attenuated FAP who show minimal polyp burden and are of advanced age may also defer decision-making about colectomy [99].

The timing of risk-reducing surgery is based on symptomatology and the number, size, and histology of polyps. Surveillance colonoscopy is not useful after numerous polyps have developed, because it is no longer possible to remove and biopsy all of them. It is appropriate for patients at this time to consult with a surgeon experienced with available options, including total colectomy and postcolectomy reconstruction techniques. Rectum-sparing surgery followed by sigmoidoscopic surveillance of the remaining rectum is an option for patients who wish to avoid total colectomy, provided they are able to understand the risks and consequences and to follow through with surveillance recommendations [99].

**Familial Colorectal Cancer**

Many families exhibit aggregation of colorectal cancer and/or adenomas in the absence of known or identifiable genetic susceptibility factors; this is termed familial colorectal cancer [100]. The presence of colorectal cancer in more than one family member may be caused by hereditary factors, shared environmental risk factors, or even chance. Familial colorectal cancer accounts for 20% of all colorectal cancer cases [78].

In the general population, 7% to 10% of individuals have a first-degree relative with colorectal cancer and 14% to 20% have either a first-degree or a second-degree relative with colorectal cancer [79; 83; 90]. A simple family history of colorectal cancer (i.e., colorectal cancer in one or more close relatives, known hereditary colon cancer absent) confers a two- to six-fold increase in risk, with degree of risk influenced by family member's age of colorectal cancer onset, the number of affected relatives, closeness of the genetic relationship, and whether colorectal cancer has occurred across generations. A positive family history of colorectal cancer appears to increase the risk of colorectal cancer earlier in life such that at 45 years of age, the annual incidence is more than three times higher than in average-risk people; at age 70 years, the risk is similar to that in average-risk individuals. The incidence in individuals 35 to 40 years of age is about the same as that of an average-risk person at 50 years of age. There is no evidence to suggest that colorectal cancer in people with one affected first-degree relative is more likely to be proximal or more rapidly progressive [79; 83; 90].

Although controlled comparisons have not been performed of genetic screening in persons with modest family history of colorectal cancer, expert opinion is fairly consistent that colorectal cancer screening should begin earlier in life (35 to 40 years of age, when risk magnitude approximates that of an individual 50 years of age). Screening in persons with average risk of colorectal cancer should begin at 50 years of age with repeat screening every 10 years. Increased risk with greater extent of family history warrants room for clinical judgment in favor of even earlier screening based on family history, and shortening the frequency of screening interval
to every five years. There is no empirical or logical support to initiate colorectal cancer screening 10 years younger in age than the family member with youngest age of colorectal cancer detection [79; 101].

Other Genetic Factors
In addition to FAP and Lynch syndrome, several rare genetic syndromes confer an increased risk for colorectal cancer, including [79; 83]:

- Peutz-Jeghers syndrome: STK11/LKB1 gene
- Juvenile polyposis syndrome: SMAD4/DPC4 and BMPR1A genes
- Cowden syndrome: PTEN gene
- Ruvalcaba-Myhre-Smith syndrome: PTEN gene
- Hereditary mixed polyposis syndrome

Factors that Suggest Hereditary Colorectal Cancer Predisposition Syndrome
With the exception of autosomal recessive inheritance with MYH-associated polyposis, all gene mutations known to cause colorectal cancer predisposition are inherited in an autosomal dominant fashion [100]. Thus, family characteristics consistent with autosomal dominant inheritance of cancer predisposition are important to identify because they indicate high risk and possibly the presence of a cancer-predisposing mutation. Factors that suggest a hereditary colorectal cancer predisposition syndrome include [99; 100]:

- Vertical transmission (i.e., presence of a genetic predisposition in sequential generations) of cancer predisposition in autosomal dominant conditions
- Inheritance risk of 50% for both men and women because when a parent carries an autosomal dominant genetic predisposition, each child has a 50% chance of inheriting the predisposition regardless of sex
- Other clinical characteristics:
  - Cancers with an earlier age of onset than sporadic (non-genetic) cases
  - Predisposition to other cancers, such as endometrial cancer
  - Two or more primary cancers in a single individual, including multiple primary cancers of the same type (e.g., two separate primary colorectal cancers) or primary cancer of different types (e.g., colorectal and endometrial cancer)
  - Presence of non-neoplastic extracolonic features, as with congenital retinal pigment epithelium hypertrophy and desmoids in FAP

Oligopolyposis (i.e., polyp count greater than expected) can involve as few as 10 to 15 polyps, and the diverse pathology of polyps requires careful attention to polyp count and histology to determine whether genetic testing and/or further clinical evaluation is appropriate [99].

Genetic Testing
As discussed, many genes associated with inherited colorectal cancer syndromes have been identified, and genetic testing is available for diagnosis and is the accepted standard of clinical care. Genetic testing of asymptomatic persons without colorectal cancer symptoms or precursors (adenomatous polyps) is performed to identify increased probability of developing colorectal cancer. Positive findings should lead to diagnostic testing to investigate the presence of occult cancer, followed by treatment if cancer or precursors are found. The intent is to prevent the development of colorectal cancer or increase the likelihood of curative outcome afforded by early detection. Patients can also use this information for decisions related to family planning, work, or retirement [8].

Disease-causing mutations can be found in most families affected by one of the inherited syndromes, and once a mutation is found in an index case of the family, relatives can be tested for the presence or absence of that mutation with near-100% accuracy. Cancer screening and management is then based on the genetic testing results [102].

Clinical issues somewhat unique to genetic testing include genetic counseling and informed consent for genetic testing. Genetic screening for inherited colorectal cancer syndromes can be hampered by patient or proband resistance, but consent to testing is greatly improved with coordination between the pathologist, referring surgeon or oncologist, and a cancer genetics counselor [85; 102].

Clinical criteria used to identify candidates for genetic testing to determine the presence of an inherited susceptibility to colorectal cancer include [79; 83; 90]:

- A strong family history of colorectal cancer and/or polyps
- Multiple primary cancers in a patient with colorectal cancer
- Family history of other cancers consistent with known inherited syndromes causing a high risk of colorectal cancer
- Early age at colorectal cancer diagnosis

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- Other clinical characteristics:
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  - Predisposition to other cancers, such as endometrial cancer
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- Multiple primary cancers in a patient with colorectal cancer
- Family history of other cancers consistent with known inherited syndromes causing a high risk of colorectal cancer
- Early age at colorectal cancer diagnosis
Screening/Surveillance Recommendations for Hereditary Colorectal Cancer

Patients diagnosed with a hereditary colorectal cancer syndrome or with a highly suggestive family or personal history require a more intensive and frequent screening and surveillance protocol than patients with average risk because of their high risk for colorectal and extracolonic malignancies. Table 3 provides a summary of recommendations for patients with specific hereditary colorectal cancer syndromes [78; 99]. For each hereditary colorectal cancer syndrome, the left column lists malignancies associated with the syndrome, and the corresponding right column describes screening or surveillance approach specific to the at-risk malignancy.

Inflammatory Bowel Disease as Colorectal Cancer Risk Factor

Patients with inflammatory bowel disease, which includes ulcerative colitis and Crohn disease, have an elevated risk of developing colorectal cancer. The extent that colorectal cancer risk is elevated depends on the extent and duration of disease, but earlier age at onset is not associated with greater risk. Older estimates of colorectal cancer risk in patients with ulcerative colitis indicated a 2% greater risk after 10 years, 7.7% to 8% after 20 years, and 15.8% to 18% after 30 years of disease [103]. More recent estimates are somewhat lower, the result of more widespread prescribing of chemoprotective aminosalicylates, earlier and more liberal use of colectomy for medically refractory disease, and higher rates of surveillance colonoscopy. Studies involving patients with either ulcerative colitis or Crohn disease have shown comparable risk in both diseases [103].

The extent of inflammatory bowel syndrome is defined as the point in time when histologically identified disease is most extensive. Most colorectal cancers develop in patients with pancolitis, and disease extent is a major risk factor for colorectal cancer in patients with inflammatory bowel syndrome [103]. Patients with left-sided disease (up to the splenic flexure) have an intermediate risk level, while proctitis, ulcerative proctosigmoiditis, and backwash ileitis have little to no influence on risk level. A family history of sporadic colorectal cancer in a first-degree relative doubles the risk of colorectal cancer, and risk increases nine-fold if the first-degree relative was younger than 50 years of age when first diagnosed with colorectal cancer.

The extent of macroscopic and histologic inflammation is associated with increased risk of colorectal cancer, which can develop in areas of endoscopically normal but histologically active colitis. Colorectal cancer can occur in areas where colitis has remitted or where histologic findings show inactive colitis such as crypt distortion in the absence of active inflammation. Lack of endoscopic inflammation at the time of neoplastic detection does not mean absence of inflammation in the area before neoplastic development, and risk of neoplasia is not increased in mucosa that has never been inflamed. Thus, histologic instead of macroscopic evidence of tissue changes from inflammatory bowel syndrome serves as a more accurate determinant for assessing colorectal cancer risk. In the context of surveillance, extent of disease should be defined histologically [103].

Practice recommendations for the diagnosis and treatment of colorectal cancer in inflammatory bowel syndrome patients were developed and published by the American Gastroenterology Association [103]. The guideline format presents a series of clinically relevant questions raised by an expert panel, followed by the response based on analysis of the published research.

Natural History of Dysplasia

Colorectal cancer in inflammatory bowel syndrome develops from dysplasia in most cases, and although imperfect, dysplasia is considered the best marker of colorectal cancer risk in inflammatory bowel syndrome. Predicting the natural history of dysplasia is more difficult, because dysplasia is present in 75% to 90% of patients with inflammatory bowel syndrome and colorectal cancer but colorectal cancer can develop in the absence of previous history of dysplasia. Not all patients with low-grade dysplasia progress through a phase of detectable high-grade dysplasia before developing cancer. Importantly, interpretation of dysplasia in mucosal biopsy specimen is highly subject to observer subjectivity. Therefore, pathologists with particular expertise in gastrointestinal disorders should review all cases diagnosed as indefinite, low-grade dysplasia, or high-grade dysplasia.

Colectomy

Strong evidence indicates that patients with inflammatory bowel syndrome and a non-adenoma-like dysplasia-associated lesion or mass should receive a colectomy. Patients with inflammatory bowel syndrome and an adenoma-like dysplasia-associated lesion or mass, without evidence of flat dysplasia elsewhere in the colon, can be managed safely by polypectomy and continued surveillance.

There is also strong evidence that colectomy for flat high-grade dysplasia treats undiagnosed synchronous cancer and prevents metachronous cancer. However, current evidence is insufficient to assess the balance of benefits and harms.

Surveillance Colonoscopy

Surveillance colonoscopy is at least moderately effective in reducing colorectal cancer risk in patients with inflammatory bowel syndrome. It is recommended for patients with inflammatory bowel disease who are at an increased risk of colorectal cancer. Patients most likely to benefit are those with extensive ulcerative colitis or Crohn disease.
### Screening and Surveillance Recommendations for Colorectal Cancer and Extracolonic Malignancies in Patients with Hereditary Colorectal Cancer Syndromes

<table>
<thead>
<tr>
<th>Cancer Screening</th>
<th>Recommendations</th>
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<tbody>
<tr>
<td><strong>Lynch syndrome/HNPCC</strong></td>
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<tr>
<td>Colorectal Colonoscopy every one to two years starting at 20 to 25 years of age or two to five years before earliest colorectal cancer in the family if diagnosed before 25 years of age</td>
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<tr>
<td>Gastric and small bowel EGD with extended duodenoscopy and polypectomy beginning at 30 years of age and repeated every two to three years</td>
<td></td>
</tr>
<tr>
<td>Urothelial Annual urinalysis</td>
<td></td>
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<tr>
<td>CNS Annual physical exam, no added screening</td>
<td></td>
</tr>
<tr>
<td>Pancreatic No recommendations</td>
<td></td>
</tr>
<tr>
<td>Endometrial and ovarian (women) Endometrial sampling and concurrent transvaginal ultrasound (preferably day 1–10 of cycle if premenopausal) annually starting at 30 to 35 years of age or 5 to 10 years prior to earliest age at first diagnosis if these cancers are in the family Prophylactic hysterectomy and bilateral salpingo-oophorectomy after childbearing is completed</td>
<td></td>
</tr>
</tbody>
</table>

**Diagnosis of familial adenomatous polyposis (FAP)**

<table>
<thead>
<tr>
<th>Cancer Screening</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal: APC gene-positive Flexible sigmoidoscopy or colonoscopy annually starting at 10 to 15 years of age Consider colectomy</td>
<td></td>
</tr>
<tr>
<td>Colorectal: Suspected FAP, not tested Flexible sigmoidoscopy or colonoscopy starting 10 to 15 years of age, then annually until 24 years of age, every two years until 34 years of age, and every three years until 44 years of age</td>
<td></td>
</tr>
</tbody>
</table>

**Personal history of FAP, post-colectomy**

<table>
<thead>
<tr>
<th>Cancer Screening</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal Endoscopic evaluation every six months to three years, depending on proctocolectomy or colectomy status NSAID chemoprevention to reduce polyp burden as pharmacologic adjunct to endoscopy</td>
<td></td>
</tr>
<tr>
<td>Duodenal, gastric, or periampullary Baseline upper endoscopy (including side-viewing exam), repeated every one to three years depending on severity of polyposis Examine stomach at time of duodenoscopy</td>
<td></td>
</tr>
<tr>
<td>Thyroid Annual thyroid exam starting in late teens</td>
<td></td>
</tr>
<tr>
<td>CNS cancer Annual physical exam, no added screening</td>
<td></td>
</tr>
<tr>
<td>Intra-abdominal desmoids Annual abdominal palpation With a family history of desmoids, consider abdominal CT or MRI every 1 to 3 years post-colectomy and then at 5- and 10-year intervals</td>
<td></td>
</tr>
<tr>
<td>Small bowel polyps and cancer Add small bowel visualization with CT or MRI for desmoids as outlined above, especially with advanced duodenal polyps</td>
<td></td>
</tr>
<tr>
<td>Hepatoblastoma (childhood cancer associated with FAP) Liver palpation, abdominal ultrasound, and measurement of α-fetoprotein every three to six months until 5 years of age FAP genetic testing in untested children with hepatoblastoma</td>
<td></td>
</tr>
<tr>
<td>Pancreatic No recommendations</td>
<td></td>
</tr>
</tbody>
</table>

**Personal history of AFAP**

<table>
<thead>
<tr>
<th>Cancer Screening</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal: &lt;21 years, small adenoma burden Colonoscopy and polypectomy every one to two years; surgical evaluation and counseling</td>
<td></td>
</tr>
<tr>
<td>Colorectal: 21–40 years, small adenoma burden Colectomy with IRA or colonoscopy and polypectomy every one to two years; surgical evaluation and counseling</td>
<td></td>
</tr>
</tbody>
</table>

*Table 3 continues on next page.*
### SCREENING AND SURVEILLANCE RECOMMENDATIONS
FOR COLORECTAL CANCER AND EXTRACOLONIC MALIGNANCIES IN PATIENTS WITH HEREDITARY COLORECTAL CANCER SYNDROMES (Continued)

<table>
<thead>
<tr>
<th>Cancer Screening</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal: &gt;40 years, small adenoma burden</td>
<td>Colectomy with IRA; surgical evaluation and counseling</td>
</tr>
<tr>
<td>Colorectal: Significant polyposis not manageable with polypectomy</td>
<td>Colectomy with IRA (preferred) or proctocolectomy with ileal J-pouch anal anastomosis</td>
</tr>
<tr>
<td>Colorectal</td>
<td>If patient had colectomy with IRS, endoscopic exam of rectum every 6 to 12 months depending on polyp burden; Annual physical exam; annual thyroid exam; NSAID chemoprevention; Baseline upper endoscopy every six months to four years starting at 25 to 30 years of age</td>
</tr>
</tbody>
</table>

#### Family history of AFAP

| Colorectal: APC positive or not tested                                         | Colonoscopy starting in late teens, then every two to three years                                |
| Colorectal: APC negative                                                      | Average risk screening                                                                           |

#### Diagnosis of MYH-associated polyposis or family history of sibling with MYH polyposis

| Colorectal: Sibling with MYH polyposis and patient is asymptomatic            | Colonoscopy starting at 25 to 30 years of age and every three to five years if negative (shorter intervals with advancing age) |
| Colorectal: MYH mutation positive or untested                                 | Upper endoscopy and side viewing duodenoscopy starting at 30 to 35 years of age and every three to five years; Patients with duodenal adenomas are treated as in FAP; Genetic counseling and testing for the familial MYH polyposis mutation(s) |

#### Personal history of MYH-associated polyposis

| Colorectal: Personal history of positive MYH mutation, polyposis, and negative APC testing | Genetic counseling and testing for MYH polyposis mutation(s); if negative, refer to increased risk colorectal cancer screening guidelines for multiple adenomatous polyps |
| Colorectal: History of adenomatous polyposis and negative APC testing (>10 at one time or >15 in 10 years) | If adenomas are manageable with colonoscopy and polypectomy:                                      |
|                                                                                   | • Colonoscopy and polypectomy every one to two years                                               |
|                                                                                   | • Upper endoscopy and side viewing duodenoscopy starting at 30 to 35 years of age and every three to five years; Patients with duodenal adenomas treated as in FAP; Genetic counseling and testing for the familial MYH polyposis mutation(s) |
|                                                                                   | If dense or large polyps are not manageable with colonoscopy and polypectomy:                     |
|                                                                                   | • Subtotal colectomy or proctocolectomy depending on adenoma density and distribution; counseling regarding surgical options |
|                                                                                   | • Upper endoscopy and side viewing duodenoscopy starting at 30 to 35 years of age and every three to five years; Patients with duodenal adenomas treated as in FAP; Genetic counseling and testing for the familial MYH polyposis mutation(s) |
|                                                                                   | • Counseling regarding surgical options                                                            |

AFAP = attenuated familial adenomatous polyposis, CNS = central nervous system, CT = computed tomography, EGD = esophagogastroduodenoscopy, FAP = familial adenomatous polyposis, HNPCC = hereditary nonpolyposis colorectal cancer, IRA = ileorectal anastomosis, MRI = magnetic resonance imaging, NSAID = nonsteroidal anti-inflammatory drug.

Source: [78; 99] Table 3
Surveillance colonoscopy in patients with inflammatory bowel syndrome should include extensive biopsies of all anatomic segments of colorectal mucosa. Definitive data are lacking to inform the optimal surveillance intervals, but one- to three-year intervals are suggested. Careful mucosal inspection and sufficient number of biopsy specimens should be obtained from all anatomic segments of the colon.

**Newer Imaging Techniques**

Chromoendoscopy is more sensitive in dysplasia detection than white-light endoscopy when used by endoscopists with expertise. However, the natural history of chromoendoscopically detected dysplasia is unknown. In addition, more research is needed to determine the utility of narrow band imaging and confocal endomicroscopy in detecting dysplasia.

**Chemopreventive Agents**

Ursodeoxycholic acid has demonstrated significant reductions in colorectal cancer in patients with ulcerative colitis who also have primary sclerosing cholangitis. Aminosalicylates are also considered chemopreventive against colorectal cancer. Oral or topical corticosteroids, while demonstrating antineoplastic effects in clinical trials, are associated with too many side effects for routine chemopreventive use. There is insufficient evidence to inform a recommendation for or against the use of azathioprine, 6-mercaptopurine, folic acid, calcium or multivitamin supplements, or statins.

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**COLORECTAL CANCER SCREENING**

**What is the preferred colorectal cancer screening modality?**

As noted, the United States is the only developed country experiencing declining incidence rates of colorectal cancer, despite the increase in colorectal cancer risk factors such as obesity [4]. Increasingly widespread colorectal cancer screening is believed to be the root of this seeming paradox.


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

Colorectal cancer is a serious disease but in many cases is preventable, and its incidence, mortality, and financial burden to society make it an important healthcare concern. The usually long and often asymptomatic premalignant natural history and the clinical features of colorectal cancer make the malignancy amenable to prevention by screening. Colonoscopy has become the dominant screening approach, and optical (versus computed tomography [CT] or “virtual”) colonoscopy has the advantage of providing cure via polypectomy during the session [104].

Evidence supports screening for colorectal cancer as part of routine care for all adults 50 years of age or older, especially those with first-degree relatives with colorectal cancer, for the following reasons [105]:

- Increased incidence in those 50 years and older
- Ability to identify high-risk groups
- Slow growth of primary lesions
- Better survival of patients with early-stage lesions
- Relative simplicity and accuracy of screening tests

Consistent evidence supports population-level colorectal cancer screening, which has become the foundation for primary colorectal cancer prevention. In a 2012 study involving 2,602 patients initially referred to colonoscopy for adenomas and nonadenomatous polyps from 1980 to 1990, participants were followed up to 23 years (median: 15.8 years). Their mortality from colorectal cancer was compared against the expected colorectal cancer mortality in the general population. Colonoscopy was associated with a 53% reduction in mortality (12 colorectal cancer death versus 25.4 expected). During the first 10 years post-polypectomy, colorectal cancer mortality was comparable between patients with adenomas or nonadenomatous polyps [106].

In another study, 46,551 healthy subjects between 50 and 80 years of age were randomized to annual or biennial fecal occult blood testing (FOBT) or no screening from 1976 to 1992. Those with positive FOBT screens received colonoscopy and treatment for malignant findings. At 30-year follow-up, 33,020 had died, 732 from colorectal cancer, including 200/11,072 (1.8%) with annual, 237/11,004 (2.2%) with biennial, and 295/10,944 (2.7%) with no screening. At 30 years, colorectal cancer mortality was reduced by 32% with annual screening and 22% with biennial screening compared with no colorectal cancer screening [107].

Researchers compared 3,148 patients with first diagnosis of colorectal cancer with 3,274 non-colorectal cancer subjects to assess associations between colonoscopy for specific indications and the risk of colorectal cancer over a 10-year period. History of screening colonoscopy was associated with a reduction of colorectal cancer risk of 89% and of malignancy in the right colon of 78%. History of diagnostic colonoscopy
(and indication) was associated with colorectal cancer risk reduction of 67% with assessment of positive FOBT; 67% with surveillance after a preceding colonoscopy; 72% with assessment of rectal bleeding; and 85% with assessment of abdominal symptoms [108].

Another large study followed 40,826 patients for a median 7.7 years to study the impact of adenoma removal during screening colonoscopy on colorectal cancer mortality. Using data from the Norway national cancer and cause-of-death registries, researchers found that, relative to expected colorectal cancer mortality (the general Norwegian population), adenoma removal during screening was associated with a 25% reduction in mortality rate [109].

Unfortunately, despite sophisticated nationwide efforts to elevate screening awareness, routine screening of eligible individuals remains low [110]. Currently, only about half of Americans 50 years of age or older, for whom screening is recommended, report having had colorectal cancer testing consistent with current guidelines [8].

To better understand potential provider and systemic obstacles to achieving higher utilization rates of colorectal cancer screening, a national survey of colorectal cancer screening education, prioritization, and self-perceived preparedness was performed of 835 primary care residents. In regards to advising patients about colorectal cancer screening, current colorectal cancer screening guidelines, and criteria for familial colorectal cancer syndromes, a significant proportion of respondents felt they lacked sufficient knowledge in these areas. These data suggest opportunities to improve the colorectal cancer screening curriculum in primary care residency programs [111].

As colonoscopy has increasingly become widespread and preferred as a colorectal cancer screening approach, questions concerning its optimal use have emerged. Research has now established that the ability of colonoscopy to detect precancerous polyps and malignant tissue critically depends on examination quality. Patient adherence to pre-colonoscopy preparation is also essential. Practice guidelines addressing these important issues have been published to bridge the knowledge gaps between the latest research, primary care, and specialist providers. Practice guidelines for colorectal cancer screening are updated as new information becomes available. For example, in 2014 the National Comprehensive Cancer Network (NCCN) expanded its recommendation for screening for Lynch syndrome to all patients diagnosed with colorectal cancer [112].

**Common Colorectal Cancer Screening Tests**

There are several screening tests available for colorectal cancer, with varying levels of efficacy and clinical utility (Table 4). Of these, the criterion standard is colonoscopy.

**Colonoscopy**

With screening colonoscopy, a colonoscope (a thin tube with a light and video camera on one end connected to a display monitor) is inserted through the rectum and guided through the length of the colon for observation on the monitor screen. Instruments to remove polyps and obtain biopsy are inserted through the rectum as needed [8]. Colonoscopy allows direct visualization of the colonic mucosa, lesion biopsy, and polypl removal over the entire colon. The sensitivity and specificity for colorectal cancer and advanced adenomas are very high, and colonoscopy is the confirmatory test used with all other screening approaches when positive findings occur [105].

**Potential Complications and Harms**

Colonoscopy may fail to detect as many as 6% of colorectal malignancies, and the miss rate for adenomas smaller than 1 cm has ranged from 12% to 17% [113]. This is largely the result of high inter-operator variability in adenoma detection rate. Greater awareness of this hazard from inadequate colonoscopy performance has led to heightened emphasis on training and continuous quality assurance of endoscopists [105]. In addition, colonoscopy is an invasive procedure, requires an invasive bowel cleansing, is time-consuming and uncomfortable, and thus possesses several characteristics that negatively affect patient acceptance as a first-line screening test [105].

Clinically significant complications that require medical intervention are rare and include perforation, bleeding, and cardiovascular events. Complication rates may increase in older patients [114; 115]. More than 85% of serious colonoscopy complications occur during polypectomy, and a study of 97,000 colonoscopies found polypectomy associated with a seven-fold increase in risk of bleeding or perforation [116]. Up to 33% of patients report one or more minor, transient gastrointestinal symptoms after colonoscopy, and a review of 12 studies involving 57,742 colorectal cancer screening colonoscopies in average-risk patients found the aggregate rate of serious complications was 2.8 per 1,000 procedures [115; 117].
## Efficacy of Colorectal Cancer Screening Tests

<table>
<thead>
<tr>
<th>Screening Approach</th>
<th>Magnitude of Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effect on colorectal cancer mortality reduction</strong></td>
<td></td>
</tr>
<tr>
<td>Fecal occult blood test (FOBT)</td>
<td>15% to 33%</td>
</tr>
<tr>
<td>Sigmoidoscopy</td>
<td>About 60% to 70% for left colon</td>
</tr>
<tr>
<td>Digital rectal examination</td>
<td>No effect</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>About 60% to 70% for left colon, uncertain for right colon</td>
</tr>
<tr>
<td><strong>Effect on surrogate endpoints (e.g., stage at diagnosis, adenoma detection)</strong></td>
<td></td>
</tr>
<tr>
<td>Sigmoidoscopy</td>
<td>45% decrease in cancer detection rate vs. colonoscopy</td>
</tr>
<tr>
<td>FOBT/sigmoidoscopy</td>
<td>No difference between sigmoidoscopy and FOBT vs. sigmoidoscopy alone</td>
</tr>
<tr>
<td>Barium enema</td>
<td>Detects 30% to 50% of cancers detected by colonoscopy</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>About 3% of patients with no distal adenomas have advanced proximal neoplasia, with a 3-fold increase in this rate in patients with distal adenomas</td>
</tr>
<tr>
<td>Computed tomography colonography</td>
<td>May have similar sensitivity to colonoscopy</td>
</tr>
<tr>
<td>Stool DNA mutation tests</td>
<td>Unknown</td>
</tr>
<tr>
<td>Immunochemical FOBT</td>
<td>60% to 90% of colorectal cancers</td>
</tr>
</tbody>
</table>

*Source: [1]*

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### Recommendations to Optimize the Adequacy of Colonoscopy Bowel Preparation

The U.S. Multi-Society Task Force on Colorectal Cancer has published guidelines for adequate pre-colonoscopy bowel cleansing [118]. The goals of this consensus document are to provide expert, evidence-based recommendations for clinicians to optimize colonoscopy preparation quality and patient safety.

The adequacy of pre-procedure bowel cleansing merits special attention because this patient factor is strongly associated with colonoscopy success. Up to 20% to 25% of colonoscopies are attempted in patients with inadequate bowel preparation, leading to diminished adenoma detection rates, longer procedural time, lower cecal intubation rates, and increased electrocautery risk [119; 120; 121].

Patient risk factors for inadequate preparation include older age, male sex, higher BMI, history of inadequate preparation, history of constipation, and use of opioids or other constipating medications. Patients with complex past medical histories or current conditions, including previous gastric or colonic resection, spinal cord injury, Parkinson disease, and stroke, are generally more difficult to prepare adequately. Diabetes is associated with the highest prevalence of inadequate bowel preparation [118].

A preliminary assessment of preparation quality should be done in the recto-sigmoid colon. If the indication is screening or surveillance and the preparation is clearly inadequate for polyp detection greater than 5 mm, terminate and reschedule the procedure or attempt an additional bowel cleansing approach without canceling the procedure that day. If the colonoscopy is complete to cecum, and the preparation ultimately is deemed inadequate, the examination should be repeated, generally within one year; intervals shorter than one year are indicated when advanced neoplasia is detected and there is inadequate preparation.

Adequacy of bowel preparation should be assessed after completing appropriate efforts to clear residual bowel debris. The rate of adequate preparation should be routinely recorded, and adequate patient preparation should be achieved in at least 85% of all examinations per physician [118].

Split-dose bowel-cleansing regimens are strongly recommended for screening colonoscopy. A same-day regimen is an acceptable alternative to split dosing, especially for patients undergoing afternoon examination. The second dose of split preparation should ideally begin four to six hours before the time of colonoscopy, with completion of the last dose at least two hours before the procedure time. With split-dose bowel-cleansing regimens, diet recommendations include low-residue or full liquids until evening on the day before colonoscopy.
Healthcare professionals should give oral and written patient instructions for all components of colonoscopy preparation and emphasize the importance of compliance. The physician performing the colonoscopy should ensure that appropriate support and process measures are in place for patients to achieve adequate colonoscopy preparation quality.

Selection of a bowel-cleansing regimen should consider patient's medical history, medications, and, when available, previously reported bowel preparation adequacy. A split-dose regimen of a 4-L polyethylene glycol electrolyte lavage solution (PEG-ELS)-based cleansing agent provides high-quality bowel cleansing. In healthy, non-constipated individuals, a 4-L PEG-ELS formulation produces a bowel-cleansing quality comparable to lower-volume PEG formulations.

Over-the-counter bowel cleansing agents have variable efficacy depending on the agent, dose, timing of administration, and whether used alone or in combination. Regardless of the agent, efficacy and tolerability are enhanced with a split-dose regimen. Although over-the-counter purgatives are generally safe, caution is required in certain populations, such as strictly avoiding magnesium-based preparations in patients with chronic kidney disease. Routine use of adjunctive agents for bowel cleansing before colonoscopy is not recommended.

Split-dose bowel cleansing is associated with greater willingness to repeat the regimen compared with day-before regimens. In addition, low-volume bowel cleansing agents are associated with greater compliance in repeat colonoscopies.

There is insufficient evidence to recommend specific bowel preparation regimens for children, adolescents, and elderly persons, but sodium phosphate preparations should be avoided in the elderly, in children younger than 12 years of age, and in those with risk factors for complications from this medication, including known or suspected inflammatory bowel disease.

Additional bowel purgatives should be considered in patients with risk factors for inadequate preparation. Low-volume preparations or extended time delivery for high-volume preparations are recommended for patients after bariatric surgery. Tap water enemas should be used to prepare the colon for sigmoidoscopy in pregnant women. There is insufficient evidence to recommend specific regimens for persons with a history of spinal cord injury; additional bowel purgatives should be considered.

There is also insufficient evidence to recommend a single salvage strategy for patients whose poor preparation precludes effective colonoscopy completion. In these cases, large-volume enemas may be attempted in patients who present for colonoscopy and report brown effluent despite compliance with the colon-cleansing regimen. Through-the-scope enema with completion of colonoscopy the same day may also be considered, especially for patients receiving propofol sedation. Waking the patient from sedation and continuing with further oral ingestion of cathartic with same-day or next-day colonoscopy is associated with better outcomes than delayed colonoscopy.

**Quality Indicators for Colonoscopy Performance**

In 2010, more than 3.3 million outpatient colonoscopies were performed in the United States, with screening and polyp surveillance accounting for roughly half [122]. In addition to patient bowel preparation, optimal colonoscopy efficacy depends on operator performance. Inadequate colonoscopy performance demonstrably worsens the ability to prevent colorectal cancer diagnoses and deaths, and practice recommendations have been developed to better ensure quality colonoscopy performance [123].

**Cecal Intubation.** Cecal intubation involves advancing the colonoscope beyond the ileocecal valve, allowing the colonoscopist to visualize the medial wall of the cecum between the ileocecal valve and the appendiceal orifice. Cecal intubation is essential for optimal colonoscopy because many colorectal neoplasms are harbored in the proximal colon, including the cecum, and low cecal intubation rates are linked to higher rates of interval proximal colon cancer [125]. Colonoscopists should be able to intubate the cecum in ≥95% of screening colonoscopies in healthy adults. Photography of the cecum is mandated to verify intubation [123].

**Adenoma Detection.** Missed adenoma detection is strongly associated with failure to prevent colorectal cancer during multi-year follow-up colonoscopy trials, and most interval colorectal cancers are due to missed lesions and incomplete polypectomy. The marked variation in colonoscopist adenoma detection rates within practice groups, and the essential role of adenoma detection in colorectal cancer prevention led to adenoma detection as a performance target [126; 127; 128]. The examination is considered adequate if detection of polyps >5 mm is unimpeded.

In screening colonoscopies of asymptomatic, average-risk persons, a minimum adenoma detection target rate of 25% is recommended. Adenoma detection rates of less than 25% indicate that performance improvement steps should be initiated. Adenoma detection rate is considered the primary measure of mucosal inspection quality and is the single most important quality measure in colonoscopy. Colonoscopists with high adenoma detection rates clear colons better, and patients with precancerous lesions are brought back earlier for their next colonoscopy. Colonoscopists with low adenoma detection rates fail to identify patients with precancerous lesions and multiple lesions, placing these patients at elevated risk for cancer from inappropriately long intervals between colonoscopy [123].
Withdrawal Time. The time taken to remove the colonoscope after cecum intubation (excluding time for biopsies or polypectomy) is termed withdrawal time, and colonic mucosa should be carefully examined for polyps during scope withdrawal. The recommended colonoscopy withdrawal time should be at least six minutes in colorectal cancer screening of patients without previous bowel surgery (when no biopsies or polypectomies are performed) [123]. Numerous studies have demonstrated increased detection of significant neoplastic lesions in colonoscopic examinations with an average withdrawal time of at least six minutes, and longer withdrawal time is associated with higher detection rates [129; 130; 131].

Correction of Poor Performance. The objective for measuring quality indicators is to improve patient care by identifying poor performers for retraining or removal of their privileges to perform colonoscopy if performance cannot be improved. Most quality indicators are amenable to improvement. An exception may be withdrawal time; despite overwhelming evidence that withdrawal time is positively associated with detection, imposing longer withdrawal times on colonoscopists has not been found effective [123].

Computed Tomographic Colonography

CT colonography, also termed virtual colonoscopy, involves examination of computer-generated colorectal images constructed from abdominal CT imaging that simulate a conventional colonoscopy. Pre-procedure laxatives are required to clean the colon, and the colon is insufflated with air just prior to the CT examination, which may be uncomfortable [132]. The risk of complications is extremely low because the test is non-invasive. CT colonography is now in use to perform screening and diagnostic imaging in patients with incomplete colonoscopy or for whom colonoscopy is contraindicated. Randomized trials are in progress comparing CT colonography with immunochemical FOBT (iFOBT) and colonoscopy, and should produce valuable information concerning patient acceptance, diagnostic yield, and costs [105].

According to the American College of Radiology, the preferred imaging modality for average-risk patients 50 years of age or older is CT colonography every five years after negative screen. (http://www.guideline.gov/content.aspx?id=47650. Last accessed March 21, 2016.)

Strength of Recommendation: 9 (Usually appropriate)

Potential Complications and Harms

Specificity for polyp detection is consistently high with CT colonography, but the broadly variable sensitivity requires confirmatory colonoscopy for findings suggestive of colorectal cancer. Another disadvantage with CT colonography is the inability to remove polyps [133]. Extracolonic abnormalities are common in CT colonography, most commonly renal, splenic, uterine, hepatic, ovarian, pancreatic, and gallbladder abnormalities. Very little information is available on the clinical value of their detection or the impact on patient anxiety and psychologic function [134; 135].

Flexible Sigmoidoscopy

Flexible sigmoidoscopy involves anal insertion of a sigmoidoscope (similar to the colonoscope) to visualize the rectum and sigmoid colon—the lower one-third of the colon. The scope inflates the large bowel with air to improve imaging, and polyp removal or biopsy may be performed during the procedure [136]. A 60-cm flexible sigmoidoscope was introduced decades ago that is more tolerable to patients than the older, rigid sigmoidoscope. It allows a more complete distal colon examination and can discover up to 65% of polyps, compared with 25% using the older instrument [137].

Potential Complications and Harms

Sigmoidoscopy can be an uncomfortable or painful procedure. Women may have more pain during the procedure, which may discourage them from returning for future screening sigmoidoscopies. Sigmoidoscopy can also cause perforation and bleeding, although this is rare [75].

Double-Contrast Barium Enema

Double-contrast barium enema (DCBE) consists of the patient receiving an enema with a barium solution. Air is then pumped into the colon, and a series of x-rays are performed to image the entire colon and rectum [8].

Potential Complications and Harms

DCBE is no longer recommended as an alternative test for colorectal cancer screening, and its use has declined dramatically. DCBE effectiveness for polyp detection is substantially lower than that of colonoscopy and CT colonography [138].

Fecal Occult Blood Tests

How do guaiac-based and immunochemical FOBTs differ?

In FOBT testing, the patient collects stool samples that are analyzed for presence of blood. Different FOBT tests involve different collection approaches but commonly require collection of consecutive stool specimens for up to three days. The first FOBTs to enter clinical use were guaiac-based (gFOBT); more recent versions employ immunochemical tests (iFOBT) or markers of DNA mutation (stool DNA tests or sDNA) [1].
Colorectal lesions and adenomatous polyps tend to bleed, and the resulting presence of hemoglobin in stool that is detectable even with intermittent or minimal bleeding formed the basis for gFOBT use in colorectal cancer screening. Hemoglobin is used as a biomarker for detecting blood in stool with guaiac, which identifies peroxidase-like activity that characterizes hemoglobin. It cannot discriminate human from nonhuman or intact from partially digested hemoglobin and is being phased out of clinical use. This results in detection of blood from ingested meat and upper airway and gastrointestinal bleeding as well as colorectal lesions. The low specificity of gFOBT requires confirmatory colonoscopy to validate positive findings [139].

iFOBT was developed to detect intact hemoglobin originating from colorectal tissue. Unlike gFOBT, it does not detect hemoglobin from nonhuman dietary sources or partly digested human hemoglobin originating from the upper respiratory or gastrointestinal tract [140]. The sDNA variation of FOBT incorporates markers of DNA mutation that detect molecular genetic changes associated with colorectal cancer gene mutations shed into the stool [141].

Potential Complications and Harms
The very low sensitivity using gFOBT leads to a high proportion of false-positive results when confirmed by colonoscopy or DCBE plus flexible sigmoidoscopy, which is a systematic review of published clinical trials estimated at greater than 80% [142]. iFOBT is increasingly recognized as superior to gFOBT for sensitivity, accuracy, and compliance, and it shows greater ability in detecting advanced neoplasia. While iFOBT requires colonoscopy confirmation of positive results and cannot detect many precancerous polyps, higher participation in iFOBT than in colonoscopy screening may offset some of its comparative limitations [105].

DNA fecal testing is emerging as a potentially important addition to the stool-based tests for colorectal cancer screening. More research is needed to understand the role of sDNA testing in organized colorectal cancer screening and unaddressed factors, such as screening interval, patient adherence, and costs [105].

PRACTICE GUIDELINE RECOMMENDATIONS FOR COLORECTAL CANCER SCREENING

American College of Physicians

The American College of Physicians (ACP) published their practice recommendations for colorectal cancer screening based on the review and synthesis of guidelines for screening colorectal cancer produced by several other professional organizations. Several tests to detect adenomatous polyps and cancer were evaluated for colorectal cancer screening efficacy, including flexible sigmoidoscopy, colonoscopy, DCBE, and CT colonography. Tests to primarily detect cancer (e.g., gFOBT, iFOBT, and sDNA) were also assessed [75].

Screening Initiation

The ACP recommends individualized assessment of colorectal cancer risk should be performed in all adults [75].

Average-risk patients should begin at 50 years of age with a stool-based test, flexible sigmoidoscopy, or optical colonoscopy. High-risk patients should begin at 40 years of age or 10 years younger than age of colorectal cancer diagnosis in the youngest family member. Test selection should be based on the benefits and harms of the specific test, the availability of the test, and patient preference. Screening is not recommended in adults older than 75 years of age or with a life expectancy of less than 10 years [75].

Note: The National Cancer Institute disputes recommendations of initiating colorectal cancer screening 10 years before the age at diagnosis in the youngest family colorectal cancer case, stating that direct evidence or strong rational argument is absent for aggressive screening methods in patients with modest family history of colorectal cancer [1].

Clinical Considerations and Best Practice Advice for Colorectal Cancer Screening

African American individuals with average risk should begin colorectal cancer screening at 40 years of age due to the higher colorectal cancer incidence and mortality rates. Healthcare professionals should consider patients’ personal, cultural, and religious preferences in screening test selection. For example, annual FOBT is not a good strategy for patients who may be unwilling or unable to follow-up yearly. Some women prefer a female endoscopist, and colonoscopy by a male endoscopist should be recommended only after discussion and patient consent.

Recommended Colorectal Cancer Screening Intervals

Patients 50 years of age or older with average risk should be screened [75]:

- Every 10 years for colonoscopy
- Every 5 years for flexible sigmoidoscopy, DCBE, and CT colonography
- Annually for gFOBT and iFOBT
- Uncertain for sDNA

These recommended intervals, especially for colonoscopy, are based on the assumption of optimal patient preparation and operator performance in the initial screen, allowing removal and biopsy of all polyps and detection of any precancerous lesion. Inadequate colonoscopy performance and resultant failure to detect adenomas or precancerous lesions places the patient at much greater risk of developing colorectal cancer (referred to as interval colorectal cancer) and renders the recommended interval unsafe [123].
Recommended Colonoscopy Surveillance after Screening and Polypectomy

What is the recommended surveillance colonoscopy interval after a baseline finding of no polyps?

The timing of follow-up surveillance colonoscopy after initial colorectal cancer screening colonoscopy is an essential component of colorectal cancer prevention (Table 5). Adenomatous polyps are cancer precursor lesions and the most common neoplasm found during colorectal cancer screening. Their detection and removal reduces colorectal cancer incidence and mortality, but patients with adenomas have heightened risk of developing interval cancers (metachronous adenomas or colorectal cancer) within three to five years of colonoscopy and polypectomy [143].

The basis for recommended time intervals between screening and surveillance colonoscopy should involve evidence that examinations prevent interval cancers and cancer-related mortality. Interval diagnosis of advanced adenomas has been used as a surrogate marker for colorectal cancer incidence or mortality. The U.S. Multi-Society Task Force guidelines for post-polypectomy surveillance in average-risk patients emphasize use of baseline colonoscopy findings for risk stratification, which is clustered into two groups [144]:

- Low-risk adenomas: One to two tubular adenomas <10 mm
- High-risk adenomas: Adenoma with villous histology, high-grade dysplasia, size ≥10 mm, or numbering three or more

The U.S. Multi-Society Task Force on Colorectal Cancer believes that patients with low-risk adenomas at baseline and negative findings at first surveillance can have their next surveillance examination at 10 years.


Level of Evidence: Moderate

The British Society of Gastroenterology surveillance guidelines categorizes patients into three risk groups [145]:

- Low risk: One to two adenomas <10 mm
- Intermediate risk: Three or four small adenomas, or one adenoma ≥10 mm
- High risk: More than five small adenomas, or three or more adenomas with at least one ≥10 mm

<table>
<thead>
<tr>
<th>RECOMMENDED SURVEILLANCE INTERVALS FOR AVERAGE-RISK PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Colonoscopy Findings</strong></td>
</tr>
<tr>
<td>No polyps</td>
</tr>
<tr>
<td>Small (&lt;10 mm) hyperplastic polyp in rectum or sigmoid</td>
</tr>
<tr>
<td>1–2 small tubular adenomas</td>
</tr>
<tr>
<td>3–10 tubular adenomas</td>
</tr>
<tr>
<td>&gt;10 adenomas</td>
</tr>
<tr>
<td>One or more tubular adenomas ≥10 mm</td>
</tr>
<tr>
<td>One or more villous adenomas</td>
</tr>
<tr>
<td>Adenoma with high-grade dysplasia</td>
</tr>
<tr>
<td>Serrated lesions</td>
</tr>
<tr>
<td>Sessile serrated polyp(s) &lt;10 mm with no dysplasia</td>
</tr>
<tr>
<td>Sessile serrated polyp(s) ≥10 mm OR sessile serrated polyp with dysplasia OR traditional serrated adenoma</td>
</tr>
<tr>
<td>Serrated polyposis syndrome</td>
</tr>
</tbody>
</table>

*Source: [143] Table 5*

Surveillance at one year was recommended for high-risk patients over concerns of missed lesions at baseline, differing from U.S. guideline emphasis (and assumption) of high-quality baseline examination [143]. This update of surveillance recommendations was developed to address emerging issues in post-colonoscopy surveillance [143].

Limitations of Colonoscopic Surveillance

As discussed, interval colorectal cancers are advanced adenomas that develop after polypectomy or negative baseline colonoscopy and before the next screening colonoscopy, a 10-year period for most patients. Within five years of negative screening colonoscopy, the risk of developing advanced adenomas is 1.3% to 2.4%. The greatest risk of interval colorectal cancer is within five years of screening colonoscopy, usually resulting from missed lesions progressing to diagnosable colorectal cancer [146].

Studies suggest that most interval colorectal cancers result from missed lesions during baseline colonoscopy. Failure to detect lesions is directly associated with colonoscopy examination quality [128; 147]. Residual neoplastic tissue from incomplete adenoma removal can also progress to malignancy. Interval colorectal cancers may differ from prevalent colorectal cancers by more frequent location in the proximal...
colon and by molecular/genetic properties that confer more aggressive growth. The relationship is established between inadequate colonoscopy quality and risk of interval cancer following colonoscopy.

**Halting Surveillance**

Colonoscopy risks increase with advancing age and at some point outweigh the benefits of surveillance and screening. The U.S. Preventive Service Task Force recommends against continued routine screening in patients 75 to 85 years of age, but decisions to continue surveillance should be individualized according to assessed benefit, risk, and comorbidity [148]. Patients with high-risk adenoma may especially benefit from continued surveillance.

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**PATHOPHYSIOLOGY**

**What are the broad colorectal carcinoma development pathways?**

The pathogenesis and pathophysiology of colorectal cancer is very complex, and the following section is intended to be a brief overview.

There are three broad pathways by which colorectal carcinoma develops [149]:

- The chromosome instability (CIN) pathway
- The microsatellite instability (MSI) pathway
- Inflammatory bowel disease dysplasia

Colorectal tumors first develop through one of these pathways, but once established as malignancy, the final common pathway to metastases is identical and involves the spread of cancer cells to locoregional lymph nodes and dissemination to and colonization of the liver (through enteric venous drainage) and the lungs (via hematogenous transport) [150].

Importantly, sporadic (i.e., in the absence of an apparent inherited disorder) colorectal cancers originating from polyps and hereditary colorectal cancers (i.e., originating from inherited colorectal cancer predisposition syndromes) share in common the sequences of gene-level altered function and mutation that transform benign tissue to precancerous lesion to malignancy. The distinction is that germline mutations underlie the well-described inherited colorectal cancer syndromes, while sporadic cancers arise from a stepwise accumulation of somatic genetic mutations [151].

With very few exceptions, the pathogenesis and pathophysiology of colon and rectal cancer is identical. Unless otherwise stated, the following information pertains to both.

**HISTOLOGICAL CHARACTERISTICS OF COLORECTAL CANCER**

**Cellular Classification**

Data from more than 169,000 patients with colorectal cancer were entered into the Surveillance, Epidemiology, and End Results (SEER) cancer database from 1991–2000 and analyzed [152]. Histologic subtypes in the population were overwhelmingly adenocarcinoma (97.4%); others included carcinoid (1.5%), malignant lymphoma (0.5%), non-carcinoid neuroendocrine (0.3%), and squamous cell (0.2%). Lymphoma was more common in men. Tumors predominantly in the colon were lymphoma, neuroendocrine, or adenocarcinoma, while tumors predominantly in the rectum were squamous or carcinoid. The relative five-year survival rates were highest for carcinoid tumors (91.3%) and lowest for neuroendocrine tumors (21.4%) [152].

**Colorectal Cancer Precursor Lesions**

**Which type of polyps have the greatest malignant potential?**

Colorectal lesions present as a broad spectrum of neoplasms that range from benign growths to invasive tumors. Most colorectal cancers develop slowly over years, typically beginning as non-cancerous polyps on the inner lining of the colon or rectum. Some, but not all, polyps develop into cancer, and the risk of malignant progression is influenced by polyp type. Colorectal lesions are classed into three groups [8; 153]:

- Adenomatous polyps (adenomas): These polyps have the greatest malignant potential and are termed pre-cancerous.
- Non-neoplastic and inflammatory polyps: These are generally not pre-cancerous, but when located in the ascending colon, the risk of pre-cancerous status or development into adenomas and cancer is increased. Includes hyperplastic, juvenile, hamartomatous, inflammatory, and lymphoid polyps.
- Dysplasia: A non-polyp pre-cancerous condition of the colorectal lining, usually associated with inflammatory bowel disease.

Adenomas are the primary precursor lesion of colorectal cancer. These polyps are benign tumors that may transform into malignancy. Of all patients with adenomatous polyps discovered by screening colonoscopy, one-year follow-up colonoscopy reveals additional polyps in 29%. The risk of colorectal malignancy in patients with history of polyp removal is 2.7 to 7.7 times that of the general population [154; 155].
Epithelial-derived adenoma or adenocarcinoma tumors represent the predominant colorectal cancer tumor type. More than 95% of colorectal cancers are carcinomas, and more than 95% of these adenocarcinomas. Other histologic types account for the remaining 2% to 5%. Adenomas are histologically classified, by order of increasing malignant potential, as tubular, tubulovillous, or villous adenomas. Characteristics of adenomas that highly predict malignant transformation include [1; 152]:

- Larger size
- Villous pathology
- Degree of dysplasia within the adenoma

Adenomas may reflect an innate or acquired tendency of the colon to form tumors. Benign and malignant tissue occurs within colorectal tumors, and 20-year follow-up of patients with adenomas has found a 25% malignancy rate in adenoma sites. Removal of adenomatous polyps is linked with reduced colorectal cancer incidence and represents the foundation of primary colorectal cancer prevention [150].

The transition from normal epithelium to adenoma to carcinoma is associated with acquired molecular events. The mucosa in the large intestine regenerates roughly every six days. Crypt cells migrate from the base of the crypt to the surface, where they undergo differentiation and maturation and ultimately lose the ability to replicate. As noted, most colorectal carcinomas are adenocarcinomas. Adenomas precede adenocarcinomas, with roughly 10% of adenomas eventually developing into adenocarcinomas during a process that occurs over up to 8 to 10 years with sporadic colorectal cancers. Dysplastic adenomas progress to colorectal malignancies through a multistep process involving inactivation of a variety of tumor-suppressor and DNA-repair genes and simultaneous activation of oncogenes. Colonic epithelial cells are selectively vulnerable to the transformation from normal colonic epithelium to adenomatous polyp to invasive carcinoma [151; 156; 157].

POLYP-TO-CARCINOMA PATHWAYS OF COLORECTAL CARCINOGEnESIS

The accumulation of acquired genetic and epigenetic changes transform normal epithelial cells into benign neoplasms (adenomas and sessile serrated polyps), invasive adenocarcinomas, and ultimately, metastatic colorectal cancer. The polyp-to-carcinoma progression sequence of colorectal carcinogenesis occurs through at least two well-recognized pathways: the CIN pathway and the MSI pathway [149].

The CIN Pathway

CIN is the most common form of genomic instability and is found in as many as 85% of colorectal cancers. The hallmark of the CIN phenotype is mutations that inactivate the APC gene, found in up to 70% of sporadic colorectal cancers and the cause FAP. APC mutations occur during the earliest stages of neoplasia and are predominantly associated with the classic tubular adenoma pathway and CIN tumor [149]. Increasing size, increasing number, and worsening histology of polyps reflect the linear process of carcinogenesis along the CIN pathway [158].

As discussed, the APC gene is a tumor-suppressor gene that indirectly regulates the transcription of several critical cell proliferation genes by encoding transcription factor beta-catenin, a protein involved in cell adhesion, signal transduction, transcription regulation, cell cycle control, apoptosis, and maintenance of chromosomal segregation fidelity. APC inactivation produces loss of beta-catenin function, allowing unchecked cellular replication at the crypt surface, and activation of oncogenes c-myc and cyclin D1 that drive the progression to malignant phenotype [90; 151; 159].

The MSI Pathway

MSI tumors are characterized by MMR system defects. DNA MMR genes correct nucleotide base miss-pairs and small insertions or deletions that occur during DNA replication. The MMR defect promotes adenoma development and accelerates the progression from adenoma to carcinoma. These colorectal malignancies are distinguished at the molecular level by alterations in repeating units of DNA that occur normally throughout the genome, termed DNA microsatellites. Microsatellite unstable tumors are generally considered mutually exclusive of CIN tumors [149; 160].

The mechanisms that underlie MSI involve MMR gene inactivation by aberrant methylation or somatic mutation. Roughly 20% to 30% of colorectal cancers display a characteristic pattern of gene hypermethylation, termed the CpG island methylator phenotype (CIMP). Some CIMP's display MSI, and these account for roughly 90% of Lynch syndrome cases and 15% to 20% of sporadic colon and rectal cancers [94; 151; 161].

THE INFLAMMATORY BOWEL DISEASE DYSPLASIA PATHWAY

A separate carcinogenic pathway is described for inflammatory bowel syndrome that does not involve an adenoma-carcinoma sequence. Chronic inflammation, such as ulcerative colitis, can result in genetic alterations that promote dysplasia and carcinoma formation [158]. The elevated risk of colorectal cancer in ulcerative colitis and Crohn disease is mediated through an intermediate step of intraepithelial dysplasia [151].
Chronic colorectal inflammatory disease is a risk factor for colorectal cancer, and such tumors may result from longstanding, continuous damage, inflammation, and repair (LOC-DIR). LOC-DIR changes cellular features of the epithelium, causing loss of cellular differentiation (loss of cellular mucus) and development of cellular atypia and mutations at multiple sites. DNA damage, with MSI and genomic instability, may arise within one year [162]. LOC-DIR may play a role in the commonly observed inactivation of Kruppel-like factor 6 (KLF-6), a tumor-suppressor gene [163].

As cellular atypia increase, there may be progression from low- to high-grade dysplasia. After 10 or more years, carcinomas may develop without an exophytic feature. After 10 years of ulcerative colitis, the risk of colorectal cancer is 20 to 30 times that for a matched population. As an effective preventive measure, most patients with ulcerative colitis undergo total colectomy with ileostomy. A more controversial but also effective procedure is proctocolectomy with ileostomy. Although Crohn disease had long been thought to lack association with the development of colorectal cancers, it is now known that there is an 8% risk of developing colorectal cancer over a 20-year period. The problem of chronic inflammation with healing and epithelial changes at the cellular and molecular levels may be involved, as most of these cancers occur in strictured areas of the large bowel [158; 162].

**SIGNALING PATHWAY Deregulation**

Important contributions to the pathogenesis of colorectal cancer come from accumulated mutations in specific genes and resultant deregulation in signaling pathways that mediate cell proliferation, differentiation, apoptosis, immortalization, angiogenesis, and invasion [149].

**Transforming Growth Factor-Beta Pathway**

Transforming growth factor-beta signaling is a tumor-suppressor pathway in the colon. Deregulation in this pathway occurs by inactivating mutations in receptor genes, post-receptor signaling pathway genes, and transforming growth factor-beta superfamily members [149; 160].

Functionally significant mutations in **TGFBR2**, a signaling receptor gene, are detected in up to 30% of all colorectal cancers. They are most common in MSI tumors but also occur in 15% of CIN tumors and are associated with transformation of late adenomas to malignancy.

**Mediators of Epidermal Growth Factor Receptor Signaling**

Mutations of PI3K pathway genes occur in up to 40% of colorectal cancer cases and may promote the transition from adenoma to carcinoma. **PTEN**, a tumor suppressor gene that negatively regulates PI3K signaling, is mutated in up to 30% of MSI tumors and 9% of CIN tumors. The PI3K pathway is modulated by epidermal growth factor receptor (EGFR) signaling in part via KRAS activation [149; 160].

The most clinically important oncogene in colorectal cancer, **KRAS** is a downstream effector of EGFR that signals (through **BRAF**) the activation of mitogen activated kinase (MAPK) pathways and promotion of cell growth and survival. KRAS mutations occur in roughly 40% of colorectal cancers, primarily in CIN tumors secondary to inactivating APC mutations [149; 160].

Mutated in roughly 10% to 15% of colorectal cancers, **BRAF** encodes a protein kinase that acts as the downstream effector of KRAS in the RAS/RAF/MAPK signaling pathway. KRAS and BRAF mutations are mutually exclusive; activating mutation in either gene is sufficient to promote tumorigenesis via increased MAPK signaling. BRAF mutations are more frequent in MSI tumors (35%) than CIN tumors (5%) [149; 160].

**PATIENT AND TUMOR CHARACTERISTICS ASSOCIATED WITH KRAS AND BRAF**

**V600E MUTATIONS IN COLON CANCER**

**KRAS** and **BRAF** mutations are important predictive and prognostic markers, respectively, in colon cancer, but until recently little has been known about the associated patient and clinical characteristics. Analysis of 2,326 patients with stage III colon cancer found that 35% showed KRAS mutations and 14% BRAF mutations, which were near-100% mutually exclusive.

KRAS mutations were more frequent in patients with negative family history of colon cancer and never smokers. Tumors with KRAS mutations were significantly less likely to have defective MMR (dMMR) and high-grade histology and were more often right-sided.

Tumors with **BRAF** mutations were more frequent in patients 70 years of age or older and current or former smokers, and less frequent in non-whites and men. Tumors with **BRAF** mutations were more frequently right-sided, with four or more positive lymph nodes, high-grade histology, and dMMR.
PROGNOSTIC/PREDICTIVE RELATIONSHIP TO GENETIC/MOLECULAR PATHOLOGY

Advances in the understanding of genetic and molecular alterations in the pathogenesis of colorectal cancer have been used to link specific gene mutations in colorectal cancer with treatment response and prognosis in colorectal cancer [149; 160; 164]:

- MSI vs. CIN: Numerous studies have established a better prognosis, independent of colorectal cancer stage, in patients with MSI tumors and unfavorable prognosis with CIN tumor.
- KRAS codon 12/13 mutations: Present in roughly 40% of colorectal cancers, strong evidence demonstrates this mutation predicts resistance to anti-EGFR therapy.
- BRAFV600E mutations: Occurring in 10% of colorectal cancers, moderate evidence suggests this mutation is likely to predict resistance to anti-EGFR therapy.
- MSI: Present in 15% of colorectal cancers, moderate evidence suggests this mutation may predict response to 5-FU and irinotecan.
- 18qLOH/SMAD4 loss: Present in 50% of colorectal cancers, moderate evidence suggests this mutation may predict resistance to 5-FU.
- COX-2 overexpression: Emerging data show colorectal cancer tumors with COX-2 overexpression are significantly associated with worse outcomes. This is consistent with the body of research associating long-term COX-2 inhibitor use with decreased rates of adenoma and colorectal cancer development and/or recurrence.

DIAGNOSIS AND STAGING OF COLON AND RECTAL CANCER

DIAGNOSTIC WORKUP

Patients with colorectal cancer typically present in one of three ways:

- Outpatients with suspicious symptoms and signs
- Asymptomatic persons discovered by routine screening
- Emergency admission with intestinal obstruction, peritonitis, or bleeding

A diagnosis of colorectal cancer is confirmed and other conditions ruled out by conducting a thorough patient history and physical examination and using appropriate testing. During the workup, the clinician should be mindful that, unless otherwise indicated, surgical resection is the first-line treatment for localized malignancy and is the only curative option for colorectal cancer. Thus, the diagnostic workup involves characterization of the malignancy and preoperative assessment.

History

Patient history and physical examination are the foundations of assessment. A thorough disease history should be obtained by eliciting disease-specific symptoms, associated symptoms, and family history. A cancer-specific history helps direct the exploration of associated pathology or metastatic disease and any further workup. When possible, all patients should undergo a full colonic evaluation with histologic assessment of the colorectal lesion before treatment. Patients should also be assessed for their fitness to undergo surgery, including assessment of cardiac risk, and preoperative radiological staging should be routinely performed [165; 166].

The incidence of colorectal cancer increases with age. Patients younger than 44 years of age account for fewer than 5% of cases, and the mean age at diagnosis is 71 years. Men and women older than 50 years of age have similar rates of colorectal cancer. However, the colorectal cancer prevalence in men increases in tandem with age beyond 50 years [84].

Physical Examination

With increasingly widespread and effective screening, colorectal cancer is frequently detected at an earlier, asymptomatic phase. Physical examination findings early in the disease course can be normal or nonspecific (e.g., fatigue, weight loss) [165; 167]. With more advanced colon cancer, common clinical presentations include iron-deficiency anemia, rectal bleeding, abdominal pain and tenderness, change in bowel habits, intestinal obstruction or perforation, hepatomegaly, and ascites. Right-sided lesions are more likely to bleed and cause diarrhea, while left-sided tumors are usually detected later and may present as bowel obstruction [165; 167].

In addition to these signs and symptoms in colon cancer, physical examination of patients with rectal cancer may reveal a palpable mass and bright red blood in the rectum. Adenopathy, hepatomegaly, or pulmonary signs may be present with metastatic rectal cancer. Proctosigmoidoscopy and digital rectal examination should be performed to determine tumor distance from the anal verge, mobility, and position relative to the sphincter complex.

Signs and Symptoms

Healthcare professionals should be attentive to both common and uncommon signs and symptoms during the history and physical exam that suggest colorectal cancer. More common diagnostic factors include increasing age, rectal bleeding, rectal mass, change in bowel habits, family history, abdominal mass or distension, and anemia [151; 168; 169; 170].
Rectal Bleeding
Although patients presenting with rectal bleeding may have a benign condition, this is a common symptom in patients with colon and rectal cancer. A primary care study found a positive correlation between each new episode of rectal bleeding in patients older than 45 years of age and colorectal cancer [170].

The Scottish Intercollegiate Guidelines Network recommends that patients older than 40 years of age who present with new onset, persistent, or recurrent rectal bleeding should be referred for investigation of possible malignancy. (http://www.guideline.gov/content.aspx?id=35211. Last accessed March 21, 2016.)

Level of Evidence: C (Evidence including well-conducted case control or cohort studies, directly applicable to the target population and demonstrating overall consistency of results, or extrapolated evidence from high-quality systematic reviews of case control or cohort studies)

Change in Bowel Habit
Especially with rectal bleeding present, an increased frequency or looser stools is common in left-sided colorectal cancer. Bowel habit changes with reduced frequency and hard stools have low predictive value for colorectal cancer.

Rectal Mass
Palpable rectal mass is present in 40% to 80% of patients with rectal cancer [171]. Assessment using digital rectal examination is useful to estimate tumor proximity to the sphincter but unreliable to determine tumor involvement of the pelvic wall and suitability for surgery. These latter investigations are more accurately assessed by magnetic resonance imaging (MRI) and transrectal endoscopic ultrasound.

Positive Family History
Although only 10% to 20% of patients with colorectal cancer have a positive family history of colorectal cancer, persons with one affected first-degree relative are more than twice as likely to develop colorectal cancer, while those with two affected first-degree relatives are four times more likely to develop colorectal cancer [78].

Abdominal Changes
The abdominal examination is typically unremarkable in patients with colorectal cancer, but the presence of a palpable tumor mass is common in advanced disease. Presence of abdominal distension indicates ascites or intestinal obstruction secondary to advanced disease. Patients are unlikely to have colorectal cancer when abdominal pain is present in the absence of other gastrointestinal symptoms, but those with colorectal cancer often have abdominal pain in addition to other symptoms.

Anemia
Anemia is present in close to 90% of patients with right-sided colon cancer at the time of diagnosis [169].

Other Signs and Symptoms
Weight loss and anorexia are more associated with advanced disease, as are palpable lymph nodes.

Endoscopic Evaluation
Patients with suspected colorectal cancer require a complete colon examination, and this is best performed with colonoscopy [172; 173]. Flexible sigmoidoscopy may be appropriate for low-risk patients, such as those with isolated rectal bleeding or who are younger than 50 years of age. However, positive findings with flexible sigmoidoscopy require pre- or postoperative confirmation and additional visualization of the entire colon, because roughly 5% of patients also harbor synchronous tumors [151; 174].

In the absence of intestinal obstruction contraindicating the administration of bowel preparation, colonoscopy is the first-line investigational choice because it demonstrates the highest sensitivity for colorectal cancer of any diagnostic modality, lacks the radiation exposure of CT, and enables the removal of incidental polyps and biopsy of suspicious lesions. The disadvantages of colonoscopy include a false-negative rate of 2% to 6% and accuracy that is highly operator-dependent and strongly influenced by patient adherence to proper preparatory bowel cleansing. Tumor localization is improved with administration of intraluminal ink or tattooing of the suspected cancer site [113; 174].

Diagnostic Imaging
CT colonography sensitivity in colorectal cancer detection is comparable to optical colonoscopy and has been used following incomplete colonoscopy assessment. DCBE has also been used in cases of poor colonoscopy visualization of the sigmoid colon (e.g., with severe diverticular disease), usually combined with flexible sigmoidoscopy. However, the superior sensitivity and specificity of CT colonography have led to the phasing out of DCBE for these indications [172; 173].
Elderly or frail patients may have difficulties with immobility or an inability to tolerate bowel preparation, which can impede conventional colonoscopy. One alternative is colorectal imaging using plain CT scan. Plain abdominal CT scan with oral contrast (but without bowel preparation) of symptomatic patients has shown an 88% to 94% sensitivity for colon cancer detection at 12- to 30-month follow-up [175; 176].

**Laboratory Tests**

Serum concentrations of carcinoembryonic antigen (CEA) are elevated in about 80% of patients with colorectal cancer, but CEA lacks sufficient sensitivity or specificity for use in screening or diagnosis. Instead, its greatest value comes from detecting colorectal cancer recurrence in patients who have undergone surgical resection. Patients should have baseline CEA values measured for comparison during the surveillance period to monitor for signs of recurrence [166].

Routine complete blood count, liver biochemistry, bone mineral density profile, and renal function are recommended before treatment to establish patient baseline values, to assess for hepatic and renal metastases, and to identify anemia [166].

**Differential Diagnosis**

During the diagnostic workup, other conditions with similarity to colon or rectal cancer should be considered and ruled out. These include [151; 167]:

- Irritable bowel syndrome
- Crohn disease
- Ulcerative colitis
- Ileus
- Diverticular disease
- Ischemic bowel
- Arteriovenous malformation
- Hemorrhoids and anal fissure

Rare gastrointestinal tumors should also be ruled out, such as:

- Carcinoid/neuroendocrine tumors
- Small-intestine carcinomas
- Gastrointestinal lymphoma

**STAGING OF COLON AND RECTAL CANCER**

Accurate staging provides crucial information about the location and size of the primary tumor, and if present, the size, number, and location of metastases. Accurate initial staging influences therapy by guiding the selection of surgical intervention and choice of neoadjuvant therapy to maximize an outcome of resection with clear margins.

**Imaging Modality**

*Which imaging modality is recommended for all patients with colorectal cancer to estimate disease stage and identify metastases?*

After colorectal cancer is diagnosed, additional imaging is required for disease staging. Liver and chest imaging, preferably using CT, is necessary to detect metastases. Rectal cancers should be staged using endorectal ultrasonography or MRI. Positron emission tomography (PET) imaging is increasingly used in colorectal cancer to detect extrahepatic metastases in patients considered for hepatic resection of presumed liver-only metastatic disease. PET is also used to localize disease in patients thought to have a recurrence, as reflected by emergent symptoms or rising CEA [151; 177; 178].

Practice guideline recommendations for imaging to stage colorectal cancer have been published by the American Society of Colon and Rectal Surgeons (ASCRS) and by Cancer Care Ontario [166; 179]. They recommend contrast-enhanced CT of the chest, abdomen, and pelvis is necessary to detect metastases. Rectal cancers should be staged using endorectal ultrasonography or MRI. Positron emission tomography (PET) imaging is increasingly used in colorectal cancer to detect extrahepatic metastases in patients considered for hepatic resection of presumed liver-only metastatic disease. PET is also used to localize disease in patients thought to have a recurrence, as reflected by emergent symptoms or rising CEA [151; 177; 178].

**Histologic Assessment**

Histologic confirmation of colon cancer is ideal, and for rectal cancer, it is essential [151]. Research has demonstrated an association between the number of lymph nodes examined in colon and rectal cancer surgery and oncologic outcomes [180]. In patients with colon or rectal cancer, the American Joint Committee on Cancer (AJCC) and National Cancer Institute jointly recommend examination of a minimum of 12 lymph nodes to rule out regional lymphatic node involvement [181].
The TNM Classification System

The AJCC has developed the TNM classification system, and this approach is the universal standard in clinical cancer care [181]. The AJCC TNM classification system is identical for colon and rectal cancer, and the same classification is used for both clinical and pathologic staging (Table 6) [165; 166]. The system was initially developed as a prognostic tool. While numerous studies have evaluated other clinical, pathologic, and molecular parameters for validity in outcome prediction, none have been validated in multi-institutional prospective trials, and the TNM system remains the only prognostic tool validated in multi-institutional prospective studies. With TNM [8]:

- T describes extent of primary tumor growth into the intestinal wall or adjacent areas. This grade reflects the extent of tumor spread in the colon and rectum wall, from the inner to the outermost layers.
- N describes the extent of primary tumor spread to nearby (regional) lymph nodes.
- M indicates whether the tumor has metastasized to other organs (most commonly, the liver or lungs)

When the T, N, and M categories have been determined (usually after surgery), the information is combined for stage grouping, with stage I the least advanced and stage IV the most advanced (Table 7) [8; 165; 166].

### AMERICAN JOINT COMMISSION ON CANCER TNM CLASSIFICATION FOR COLON AND RECTAL CANCER

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Tumor (T)</strong></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor extends through the mucosa and into the submucosa</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor extends through the submucosa and into muscularis propria</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor extends through the muscularis propria and into the subserosa but not to any neighboring organs or tissues</td>
</tr>
<tr>
<td>T4a</td>
<td>Tumor penetrates to the surface of the visceral peritoneum</td>
</tr>
<tr>
<td>T4b</td>
<td>Tumor directly invades or is adherent to adjacent organs or structures</td>
</tr>
<tr>
<td><strong>Regional Lymph Node Involvement (N)</strong></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>No regional nodal involvement</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in 1–3 regional lymph nodes</td>
</tr>
<tr>
<td>N1a</td>
<td>Metastasis in 1 regional lymph node</td>
</tr>
<tr>
<td>N1b</td>
<td>Metastasis in 2–3 regional lymph nodes</td>
</tr>
<tr>
<td>N1c</td>
<td>Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolorectal tissues without regional nodal metastasis</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in 4 or more regional lymph nodes</td>
</tr>
<tr>
<td>N2a</td>
<td>Metastasis in 4–6 regional lymph nodes</td>
</tr>
<tr>
<td>N2b</td>
<td>Metastasis in 7 or more regional lymph nodes</td>
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<tr>
<td><strong>Distant Metastasis (M)</strong></td>
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</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>M1a</td>
<td>Metastasis confined to one organ or site</td>
</tr>
<tr>
<td>M1b</td>
<td>Metastasis in more than one organ/site or the peritoneum</td>
</tr>
</tbody>
</table>

*Source: [181]*

(Table 6)
<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis, N0, M0</td>
<td>Tumor is in the earliest stage and has not grown beyond the colon or rectum mucosa. Also termed carcinoma in situ.</td>
</tr>
<tr>
<td>Stage 1</td>
<td>T1–2, N0, M0</td>
<td>Tumor extends through the muscularis mucosa into the submucosa (T1) or into the muscularis propria (T2).</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T3, N0, M0</td>
<td>Tumor extends into the outermost layers of the colon or rectum but not beyond (T3).</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T4a, N0, M0</td>
<td>Tumor extends through the wall of the colon or rectum but not into adjacent tissues or organs (T4a).</td>
</tr>
<tr>
<td>Stage IIC</td>
<td>T4b, N0, M0</td>
<td>Tumor extends through the wall of the colon or rectum and is attached to or has grown into adjacent tissues or organs (T4b).</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T1–2, N1, M0</td>
<td>Tumor extends through the mucosa into the submucosa (T1) or into the muscularis propria (T2). It has spread to 1–3 regional lymph nodes (N1a/N1b) or into areas of fat near regional lymph nodes but not into the nodes (N1c).</td>
</tr>
<tr>
<td></td>
<td>T1, N2a, M0</td>
<td>Tumor extends through the mucosa into the submucosa (T1) and has spread to 4–6 regional lymph nodes (N2a).</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T3–4a, N1, M0</td>
<td>The cancer has grown into the outermost layers of the colon or rectum (T3) or through the visceral peritoneum (T4a) but has not reached nearby organs. It has spread to 1–3 regional lymph nodes (N1a/N1b) or into areas of fat near regional lymph nodes but not into the nodes (N1c).</td>
</tr>
<tr>
<td></td>
<td>T2–3, N2a, M0</td>
<td>The cancer has grown into the muscularis propria (T2) or into the outermost layers of the colon or rectum (T3). It has spread to 4–6 regional lymph nodes (N2a).</td>
</tr>
<tr>
<td></td>
<td>T1–2, N2b, M0</td>
<td>The cancer has grown through the mucosa into the submucosa (T1) or it may also have grown into the muscularis propria (T2). It has spread to 7 or more regional lymph nodes (N2b).</td>
</tr>
<tr>
<td>Stage IIIC</td>
<td>T4a, N2a, M0</td>
<td>The cancer has grown through the wall of the colon or rectum (including the visceral peritoneum) but has not reached nearby organs (T4a). It has spread to 4–6 regional lymph nodes (N2a).</td>
</tr>
<tr>
<td></td>
<td>T3–4a, N2b, M0</td>
<td>The cancer has grown into the outermost layers of the colon or rectum (T3) or through the visceral peritoneum (T4a) but has not reached nearby organs. It has spread to 7 or more regional lymph nodes (N2b).</td>
</tr>
<tr>
<td></td>
<td>T4b, N1–2, M0</td>
<td>The cancer has grown through the wall of the colon or rectum and is attached to or has grown into other nearby tissues or organs (T4b). It has spread to at least one regional lymph node or into areas of fat near the lymph nodes (N1 or N2).</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>Any T, Any N, M1a</td>
<td>The cancer may or may not have grown through the wall of the colon or rectum, and it may or may not have spread to regional lymph nodes. It has spread to one distant organ or set of lymph nodes (M1a).</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>Any T, Any N, M1b</td>
<td>The cancer may or may not have grown through the wall of the colon or rectum, and it may or may not have spread to regional lymph nodes. It has spread to more than one distant organ or set of lymph nodes, or it has spread to distant parts of the peritoneum (M1b).</td>
</tr>
</tbody>
</table>

Source: [8; 165; 166]
In rectal cancer, AJCC staging does not apply to the following malignant histologies [182]:

• Sarcoma
• Lymphoma
• Carcinoid tumors
• Melanoma

PROGNOSTIC FACTORS

PROGNOSTIC FACTORS ASSOCIATED WITH STAGING

As discussed, KRAS mutations are present in 40% of colon adenocarcinomas and affect sensitivity to treatment with biologic agents directed against EGFR. The FDA has approved a qualitative real-time polymerase chain reaction assay, the therascreen KRAS RGQ PCR Kit, for detection of specific mutations in the KRAS oncogene [183].

dMMR is associated with high-frequency MSI instability (H-MSI), a predictor of better clinical outcomes for resectable colon cancer based on analysis of several large trials. In addition, patients with dMMR (H-MSI) do not appear to benefit from 5-FU-based adjuvant therapy [184; 185].

Testing for dMMR with H-MSI may become useful for prognosis and treatment planning in patients with resectable colon cancer. Some research also emphasizes the role of immune regulation in the natural course and prognosis of patients with colorectal cancers [186].

MOLECULAR AND CLINICAL PROGNOSTIC FACTORS

Which clinical features are associated with worse prognosis of colorectal cancer?

There are a variety of molecular/genetic and clinical factors that impact the disease course and prognosis. Molecular prognostic factors include [187]:

• p53
• Loss of heterozygosity for 18q
• Mutations of deleted in colon cancer (DCC) gene
• EGFR gene amplification

Specific clinical features associated with worse prognosis are [187]:

• Bowel obstruction at diagnosis
• Ulcerative growth pattern
• Perforation
• Elevated preoperative CEA level

HISTOLOGIC SUBTYPES AS PREDICTORS OF METASTASES

A study of autopsy results from 1,675 patients with metastasized colorectal cancer and from 88 patients with synchronous metastases observed that histologic subtype and localization of the primary colorectal cancer tumor strongly influenced metastatic pattern [188]. Metastatic disease was more prevalent, and more frequent in multiple sites, in patients with mucinous adenocarcinoma (33.9% and 58.6%, respectively) or signet-ring cell carcinoma (61.2% and 70.7%) than with adenocarcinoma (27.6% and 49.9%) [188]. Liver metastases were more frequent in patients with adenocarcinoma (73.0%) or mucinous adenocarcinoma (52.2%) than in those with single-ring cell carcinoma (31.7%). Peritoneal metastases were more common in patients with single-ring cell carcinoma (51.2%) or mucinous adenocarcinoma (48.2%) than in those with adenocarcinoma (20.1%) [188]. Metastases to distant lymph nodes occurred in more single-ring cell carcinoma patients (43.9%) than patients with either mucinous adenocarcinoma (22.3%) or adenocarcinoma (19.9%). Abdominal metastases were more frequent with colon cancer, and extra-abdominal metastases more common with rectal cancer [188].

PROGNOSTIC FACTORS FOLLOWING RESECTION OF LIVER METASTASES

Approximately one in three patients who undergo resection for colorectal liver metastases become actual five-year survivors. Of those, approximately half survive 10 years and are considered “cured” of colorectal liver metastases [189]. A multivariate analysis of 1,001 patients who underwent potentially curative resection of liver metastases identified five factors as independent predictors of worse outcome [190]:

• Tumor size >5 cm
• Disease-free interval less than one year
• More than one tumor
• Primary lymph-node positivity
• CEA level >200 ng/mL

SURVIVAL

Prognostic Factors of Survival by TNM Stage

Patient prognosis is most powerfully associated with clinical and histopathologic stage of colorectal cancer at diagnosis as reflected by the TNM classification and staging. Data obtained from the National Cancer Institute SEER database in patients diagnosed from 2004–2010 found five-year survival rates of 92% for earliest stage colon cancer and 87% for earliest stage rectal cancer (Table 8) [8].
## Colorectal Cancer Five-Year Survival Rates by Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon cancer</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>92%</td>
</tr>
<tr>
<td>IIA</td>
<td>87%</td>
</tr>
<tr>
<td>IIIB</td>
<td>63%</td>
</tr>
<tr>
<td>IIIA</td>
<td>89%</td>
</tr>
<tr>
<td>IIIIB</td>
<td>69%</td>
</tr>
<tr>
<td>IIIC</td>
<td>53%</td>
</tr>
<tr>
<td>IV</td>
<td>11%</td>
</tr>
<tr>
<td>Rectal cancer</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>87%</td>
</tr>
<tr>
<td>IIA</td>
<td>80%</td>
</tr>
<tr>
<td>IIB</td>
<td>49%</td>
</tr>
<tr>
<td>IIIA</td>
<td>84%</td>
</tr>
<tr>
<td>IIIIB</td>
<td>71%</td>
</tr>
<tr>
<td>IIIC</td>
<td>58%</td>
</tr>
<tr>
<td>IV</td>
<td>12%</td>
</tr>
</tbody>
</table>

*Source: [8] Table 8*

However, these figures are based on a previous staging system, so they can be difficult to apply to the current system. At the time, there was no stage IIC; these cancers were classed stage IIB. Some cancers now classed as stage IIIC were classed as stage IIIB, and vice versa [8].

### Other Prognostic Factors of Survival

Several other factors have shown prognostic significance, including the number of harvested and processed lymph nodes, histologic grade, and evidence of lymphovascular and perineural invasion. In patients with metastatic colorectal cancer, the level of circulating tumor cells measured at baseline after the initiation of new therapy was an independent predictor of survival. In patients with baseline CEA values ≥25 ng/mL, those with low baseline levels of circulating tumor cells (fewer than three) had longer survival, and measurements of both circulating tumor cell number and CEA level at 6 to 12 weeks independently predicted survival [191].

### Treatment of Colon and Rectal Cancer

#### Mechanism of Chemotherapy and Targeted Therapies

The chemotherapy agent 5-FU entered clinical use for patients with colorectal cancer more than 40 years ago and remains a mainstay of colorectal cancer treatment today. In the mid-1990s, the drugs irinotecan hydrochloride and oxaliplatin became available for colorectal cancer, and standard chemotherapy regimens were refined through extensive trials. Patients with metastatic colorectal cancer unsuitable for surgery represent more than 50% of those diagnosed with disseminated disease, and while they did benefit, the modest increases in life expectancy came with substantial toxicities. These patients, and their overall prognoses, remained poor. The therapeutic outlook improved with introduction of bevacizumab, the first FDA-approved antiangiogenic agent for metastatic colorectal cancer. Several additional targeted biologic agents have received FDA approval for metastatic colorectal cancer. As of 2016, these include cetuximab, panitumumab, ziv-aflibercept, and regorafenib [192; 193].

EGFR is a glycoprotein with three primary components: an extracellular ligand binding domain, a hydrophobic transmembrane domain, and an intracellular tyrosine kinase domain. EGFR is activated by ligand binding from EGF or transforming growth factor-alpha, which triggers downstream activation in signaling pathways that facilitate development and progression of colorectal cancer. This critical role of EGFR in oncogenesis has made it an attractive target for colorectal cancer therapy, and the targeted biologic agents cetuximab and panitumumab primarily act through binding EGFR to inhibit downstream signaling [149; 194].

Colorectal tumors that grow beyond 1–2 mm³ require increased access to oxygen and nutrients and develop neoangiogenesis to enable tumor growth and metastases. Neoangiogenesis originates from complex interactions between pro- and anti-angiogenic factors. Vascular endothelial growth factor (VEGF), the most potent pro-angiogenic factor known to date, is overexpressed in gastrointestinal tumors and is essential for the proliferation and metastases of colorectal cancer [195]. VEGF overexpression is associated with increased tumor vascularity, proliferation, progression, invasion, and metastasis. VEGF binds to and activates one of the three VEGF receptors located on the vascular endothelium. Among the VEGF receptor types, VEGFR-2 is the primary mediator of the mitogenic and angiogenic effects of VEGF, while VEGFR-3 is involved in lymphangiogenesis [192].
Following VEGF binding, VEGF receptors activate several downstream intracellular signal transduction pathways that promote inhibition of apoptosis, degradation of the extracellular matrix to facilitate endothelial cell proliferation and migration to form new blood vessels, and stimulation of mitosis and cytoskeletal changes associated with motility. Colorectal tumors also express VEGF and other proangiogenic factors on their cell surface; their presence is associated with increased vascularity, advanced disease, and poor prognosis [195].

Findings of elevated VEGF levels in patients with metastatic colorectal cancer led to the development and FDA approval of several anti-VEGF agents. In addition to the therapeutic targeting of VEGF, VEGF antagonists have also shown the ability to increase intratumoral delivery of chemotherapeutic agents to improve their antitumor efficacy [192].

Secondary Drug Resistance

Patients with chemotherapy-refractory colorectal cancer who initially respond and then become resistant to cetuximab or other monoclonal antibodies have essentially run out of therapeutic options. This emergence of secondary drug resistance within 9 to 18 months of initiation is a major limitation of anti-EGFR therapies. A substantial proportion of patients with colorectal cancer who initially respond to anti-EGFR therapies have, at the time of disease progression, tumors with focal amplification or somatic mutations in KRAS that were undetectable before initiation of anti-EGFR therapy. Drug-resistant KRAS alteration results from pre-existent KRAS mutant and amplified clones and from new mutations arising from ongoing mutagenesis [196]. A mechanism by which KRAS mutation nullifies anti-EGFR therapy involves bypassing the need for upstream EGFR signals to activate downstream oncogenic processes [149; 160]. It is now established that patients with any KRAS or NRAS mutation should not be treated with cetuximab or panitumumab, as these mutations strongly predict resistance to EGFR inhibitor agents. In contrast, non-mutational KRAS, termed wild-type KRAS, responds to targeted therapy [99].

GENERAL APPROACH TO TREATMENT

Overall, there is a substantial overlap between treatment approaches for colon and rectal cancer, especially in stage IV and metastasized cancer. Treatment approaches for stage I–III cancer (earlier stage) differ the most. In this section, treatment of earlier-stage colon and rectal cancer are discussed separately, and discussion of metastatic colon and rectal cancer is combined. For both cancers, the foundation of care is surgical resection for patients with local or locally advanced tumor, and chemotherapy for stage IV, metastatic, and recurrent tumor. Unlike rectal cancer, radiotherapy has limited use in colon cancer.

The timing of chemotherapy and/or radiotherapy is sequenced in relation to surgery as follows:

- Neoadjuvant chemotherapy and/or radiation therapy: Delivered before surgery, to downsize the tumor. Most often used in rectal cancer.
- Adjuvant chemotherapy and/or radiation therapy: Delivered following surgery with the intent to destroy remaining local or micro-metastasized malignant cells and colonies.
- Palliative chemotherapy or radiotherapy: Delivered to downsize or eradicate colorectal cancer tumors that have metastasized to other organs. The objective is to relieve symptoms and pain, instead of cure or prolonging survival.
- Liver metastases: The liver is the most common site of metastatic colon and rectal cancer. Treatment of hepatic metastases of primary colorectal cancer can involve surgery with neoadjuvant or adjuvant chemotherapy, local ablation, or intra-arterial chemotherapy.

The use of chemotherapy in stage IV, metastatic, or recurrent disease involves the combination of agents. A number of chemotherapy regimens have been evaluated and represent the core of therapy. Newer biologically targeted agents are added to the established chemotherapy regimens to gain the advantage of synergistic drug action, and NCCN guidelines recommend the use of as many chemotherapy drugs as possible to maximize the effect of adjuvant therapies for colon and rectal cancer [197; 198].

Several practice guidelines for the treatment of colon and rectal cancer are available and are updated and revised on a regular basis. The importance of guideline-adherent treatment was underscored by a 2015 study of all patients receiving primary treatment for colorectal cancer in a major academic medical center between 2003 and 2010. The results showed that treatment non-adherent to NCCN guidelines was associated with 3.6 times the risk of death in the first year after diagnosis and an 80% increased risk of death after two to five years. The authors state that while medically justifiable reasons for guideline deviation do occur, the overall impact on patients is a markedly greater risk of death, especially in the first year following diagnosis [199].
TREATMENT OF COLON CANCER, STAGES I–III

What is the standard treatment option for stage II colon cancer?

The standard treatment options for colon cancer are [180]:

- Stage 0: Surgery
- Stage I: Surgery
- Stage II: Surgery
- Stage III: Surgery, adjuvant chemotherapy
- Stage IV and recurrent: Surgery, chemotherapy, and targeted therapy

Surgical Resection

Treatment of localized and locally advanced colon cancer primarily involves surgical resection, and roughly 80% of colon cancer patients exhibit localized disease amenable to resection with curative intent [166]. Aside from palliative resection (e.g., alleviating obstruction), the objective of surgery is curative resection based on clear macroscopic and histological resection margins. Practice recommendations from the ASCRS were published to optimize surgical care of these patients (Table 9) [166].

The primary treatment for localized resectable colon cancer is colectomy with en bloc removal of all associated regional lymph nodes and involved adjacent structures. The extent of a curative resection for colon cancer depends on the site of the primary lesion and lymphovascular drainage of the cancer site. The length of bowel resected is governed by the blood supply to that segment. In the absence of synchronous pathology, an anatomic colon resection for cancer should achieve at least a 5-cm negative margin on either side of the tumor. Colectomy with local excision is not adequate for curative resection, because it increases risks of tumor spillage into the peritoneal cavity and tumor progression from lack of lymphadenectomy [166; 197].

Surgery is curative in 25% to 40% of highly selected patients who develop resectable metastases in the liver and lung. Refinements in surgical technique and preoperative imaging have improved patient selection and resection outcomes [180; 200; 201; 202].

Before surgery, all patients should be given information about the likelihood of having a stoma, why it might be necessary, and how long it might be needed. A trained stoma professional should provide specific information on the care and management of stomas to all patients considering surgery that might result in a stoma [203].

Post-Resection Staging

Given that tumor depth, nodal metastasis, and distant metastasis strongly predict post-surgical prognosis in colon cancer, staging should be performed following surgical resection using TNM staging, histologic grade of the tumor, and resection completeness [166].

Adjuvant Chemotherapy

Stage II

The value of adjuvant chemotherapy for stage II colon cancer is controversial. In one study, adjuvant 5-FU-based chemotherapy was evaluated in patients with high-risk stage II colon cancer following curative resection. Compared with surgery alone, adjuvant 5-FU showed inconsistent benefit; these and other results led to guidelines issued by the American Society of Clinical Oncology (ASCO) stating that evidence does not support the routine use of adjuvant chemotherapy for patients with stage II colon cancer [204; 205].

The NCCN guideline also states there is no survival advantage by adding oxaliplatin to 5-FU/leucovorin, including in patients 70 years of age or older [197]. The combination of folic acid, 5-FU, and oxaliplatin (FOLFOX) is considered reasonable in high-risk cases, but it is not indicated in good-to-average-risk stage II cancers.

Stage III

Stage III colon cancer denotes lymph node involvement. Studies have shown that prognosis is related to the number of involved lymph nodes; patients with one to three involved nodes have a significantly better survival than those with four or more involved nodes. Before 2000, 5-FU was the only adjuvant chemotherapy with activity in stage III colon cancer. With patients in many earlier trials of adjuvant 5-FU not showing a survival benefit, modifications and additions to the core 5-FU therapy were investigated in stage III colon cancer. More recently, capecitabine was established as comparable to 5-FU/leucovorin. The addition of oxaliplatin to 5-FU/leucovorin (FLOX) improved overall survival compared with 5-FU/leucovorin alone and has become the reference standard for the future generation of clinical trials for stage III colon cancer [180; 197; 206].
# ASCRS Guidelines for Surgical Management of Colon Cancer

## Surgical Treatment of the Primary Tumor

A thorough surgical exploration should be performed and documented. The extent of colon resection should correspond to the lymphovascular drainage of the colon cancer site. The lymphadenectomy should be complete and en bloc with (i.e., at the same time as) the bowel segment. Clinically positive lymph nodes located outside the standard field of resection identified at the time of resection and suspected to contain metastatic disease should be biopsied or removed at the time of primary resection. Resection of involved adjacent organs should be en bloc. Synchronous colon cancers can be treated by two separate resections or subtotal colectomy. Sentinel lymph node (SLN) mapping for colon cancer does not replace standard lymphadenectomy. Laparoscopic and open colectomy achieve equivalent oncological outcomes for localized colon cancer. The use of the laparoscopic approach should be based on the surgeon’s documented experience in laparoscopic surgery as well as on patient- and tumor-specific factors. Treatment of the malignant polyp is determined by the morphology and histology of the polyp.

## Prophylactic Oncological Resection of Extraintestinal Organs

Oophorectomy is advised for grossly abnormal ovaries or contiguous extension of the colon cancer, but routine prophylactic oophorectomy is not necessary.

## Management of Synchronous Stage IV Disease

Resectable stage IV disease: The treatment of patients with resectable stage IV colon cancer should be individualized based on comprehensive multidisciplinary evaluation. Unresectable stage IV disease: Palliative intervention or resection of the symptomatic primary tumor should be considered, but routine resection of the asymptomatic primary tumor is not recommended.

## Tumor-Related Emergencies

Bleeding: Surgical resection to stop severe blood loss from localized colon cancer should follow the same oncological principles as in elective resection. Perforation: Perforation is a life-threatening complication. After resuscitation of the patient, surgical resection to address both the perforation and the tumor should be performed, if at all possible. Obstruction: The management of patients with an obstructing cancer should be individualized but may include a definitive surgical resection with primary anastomosis.

## Management of Locoregional Recurrence

The treatment of patients with locoregionally recurrent colon cancer should be multidisciplinary, and curative resection should adhere to the principles of primary resection.

## Management of Peritoneal Carcinomatosis

The treatment of patients with peritoneal carcinomatosis should be multidisciplinary and individualized and may include surgical cytoreduction (debulking). The role of intraperitoneal chemotherapy remains insufficiently defined.

## Palliative Procedures

In patients with extensive incurable extent of tumor burden, palliative surgical interventions should be individualized based on the presence of symptoms.

## Adjuvant Therapy

Adjuvant chemotherapy may be considered for patients with high-risk stage II colon cancer. Adjuvant chemotherapy should be recommended for patients with stage III colon cancer.

*Source: [166]*

Table 9
For stage II/III colon cancer, the NCCN asserts that adjuvant bevacizumab, cetuximab, panitumumab, or irinotecan should not be used outside of clinical trials [197]. In stage III colon cancer, FOLFOX is superior to 5-FU/leucovorin, and capecitabine/oxaliplatin (CapeOx) is superior to bolus 5-FU/leucovorin. FLOX is an alternative to FOLFOX or CapeOx, but FOLFOX or CapeOx are preferred [197].

**Adjuvant Radiation Therapy**

Unlike in rectal cancer, the role of adjuvant radiation therapy is poorly defined in colon cancer treatment. Radiation therapy has no current adjuvant role following curative resection but may have a potential role in patients with residual disease [197]. If used, radiation fields should include the tumor bed, as defined by preoperative radioimaging or surgical clips. Radiation should be given in doses of 45–50 Gy in 25 to 28 fractions; the dose in the small bowel should be no greater than 45 Gy [197]. Neoadjuvant chemoradiotherapy that includes 5-FU should be delivered concurrently to aid resectability. Conformal external beam radiation is preferred; intensity-modulated radiation therapy should be limited to unique clinical situations. Intraoperative radiation therapy should be considered in T4 or recurrent cancer.

**TREATMENT OF RECTAL CANCER, STAGES 0–III**

The standard treatment options for rectal cancer are [182]:

- **Stage 0**: Polypectomy or surgery
- **Stage I**: Surgery with or without chemoradiation therapy
- **Stage II and III**: Surgery, neoadjuvant chemoradiotherapy, short-course neoadjuvant radiotherapy, and adjuvant chemoradiotherapy
- **Stage IV, metastatic, and recurrent**: Surgery with or without chemotherapy or radiotherapy, chemotherapy, and targeted therapy

Approximately 28% of colorectal malignancies are attributable to rectal carcinoma. Although surgical resection is the only curative option for rectal cancer, complete resection is rendered technically difficult by the lack of serosa covering the rectum and proximity of the rectum to the bony pelvis and other pelvic organs. Local tumor invasion is promoted by this extra-colorectal proximity to other organs, which, along with surgical difficulty, contributes to high local recurrence rates [165].

Compared to colon cancer, the increased risk of local recurrence and poorer overall prognosis in rectal cancer has led to differences in the management of localized or locally advanced disease, including greater emphasis on multimodal treatment to minimize morbidity, decrease recurrence risk, and prolong survival. Other differences in rectal cancer treatment include surgical techniques, use of radiation therapy, and chemotheraphy protocol. In stage II or III rectal cancer, neoadjuvant therapy is now favored over adjuvant therapy based on evidence of improved local control and increased rates of sphincter preservation [207; 208; 209].

An important consideration is the impact of rectal cancer surgery on the structure and function of adjacent sensitive tissues, and the therapeutic issues related to the maintenance or restoration of normal anal sphincter, genitourinary, and sexual function [210; 211]. Practice recommendations for the surgical treatment of localized rectal cancer have been published by the ASCRS (Table 10) [165].

Treatment of rectal cancer is determined by clinical disease stage and the risk of local recurrence. Low-risk, early-stage disease is generally treated with primary surgical therapy, while locally advanced or high-risk disease requires multimodality therapy that includes neoadjuvant radiation or chemoradiation [165]. The risk of local recurrence is estimated using MRI imaging before surgical intervention. Risk level is defined as low, moderate, or high based on the following criteria [212]:

**Low Risk**
- Clinical stage T1, T2 or T3a, AND
- No lymph node involvement

**Moderate Risk**
- T3b or greater, in which the potential surgical margin is not threatened, OR
- Any suspicious lymph node not threatening surgical resection margins, OR
- The presence of extramural vascular invasion

**High Risk**
- A threatened (<1 mm) or breached resection margin, OR
- Low tumors encroaching onto the intersphincteric plane or with levator involvement
## ASCRS GUIDELINES FOR SURGICAL MANAGEMENT OF RECTAL CANCER

### Surgical Techniques and Operative Considerations, Local Excision

Local excision is appropriate for carefully selected T1 rectal cancers without high-risk features.

### Surgical Techniques and Operative Considerations, Radical Excision

A thorough surgical exploration should be performed and the findings documented in the operative report. Total mesorectal excision should be used for curative resection of tumors of the middle and lower thirds of the rectum, either as part of low anterior or abdominoperineal resection. For tumors of the upper third of the rectum, a tumor-specific mesorectal excision should be used with the mesorectum divided ideally no less than 5 cm below the lower margin of the tumor.

A 2-cm distal mural margin is adequate for most rectal cancers when combined with a total mesorectal excision.

For cancers located at or below the mesorectal margin, a 1-cm distal mural margin is acceptable.

Proximal vascular ligation at the origin of the superior rectal artery with resection of all associated lymphatic drainage is appropriate for most rectal cancer resections.

In the absence of clinical involvement, extended lateral lymph node dissection is not necessary in addition to total mesorectal excision.

### Tumor-Related Emergencies

In patients with large-bowel obstruction, an expanding stent is an acceptable treatment option in the palliative setting or as a bridge to definitive resection.

### Multimodality Neoadjuvant Therapy

Neoadjuvant therapy should be used for locally advanced cancers of the mid or distal rectum.

### Multimodality Adjuvant Therapy

Adjuvant chemoradiotherapy should be recommended for select patients with stage III or high-risk stage II rectal cancer who have not received neoadjuvant therapy.

Adjuvant chemotherapy should be recommended for patients with high-risk stage II and all stage III disease previously treated with neoadjuvant therapy.

### Source: [165]

### Table 10

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### Primary Surgical Therapy

Rectal cancer surgery involves surgical resection of the primary tumor. Surgical approach is guided by tumor location, disease stage, and presence of high-risk features (e.g., positive margins, lymphovascular invasion, perineural invasion, poorly differentiated histology) [182].

Polypectomy alone may be sufficient when polyps with invasive cancer can be completely resected with clear margins and show favorable histologic features, generally select T1 cancers [213]. Approaches with minimal morbidity and mortality include transanal excision and transanal endoscopic microsurgery. Local excision is appropriate in selected T1 tumors, with mesorectal excision preferred for all other T1–T2/N0 tumors. Endoscopic microsurgery cannot perform excision and staging of mesorectal lymph nodes, a limitation because T1 lesions have a 6% to 11% risk of harboring nodal metastasis [214]. Local recurrence rates range from 7% to 21% for T1 lesions and 26% to 47% for T2 lesions [214; 215; 216].
Total mesorectal excision with autonomic nerve preservation via low-anterior resection is preferred, followed by colorectal anastomosis in advanced mid- to upper-rectal tumor. Low anterior rectal resection is associated with bowel urgency, increased bowel frequency, clustering, and fecal incontinence from loss of rectum reservoir function. The colonic J-pouch is the superior approach for improving postoperative bowel function [51; 217]. In patients unsuitable for sphincter-preservation, total mesorectal excision via abdominoperineal resection is preferred, although this leaves patients with a permanent colostomy [218; 219; 220].

Despite the low rate of local relapse after meticulous mesorectal excision, the heightened tendency for first failure to solely occur in locoregional sites requires the ongoing routine use of adjuvant radiation therapy [165].

Multimodality Therapy
Multimodality therapy has been the standard of care for patients with locally advanced rectal cancer since 1990, when the National Cancer Institute recommended adjuvant therapy for stage II and III disease [221]. This was based on findings of 33% to 55% reduction in local recurrence and significant prolongation in disease-free survival. Although the National Cancer Institute recommended adjuvant therapy, subsequent findings have shown superior efficacy, lower toxicity, and better long-term outcomes with neoadjuvant therapy [222; 223; 224].

Preoperative radiation therapy is more effective because well-oxygenated tissue responds better to irradiation; postoperative tissue is relatively hypoxic from surgery and may be more resistant to radiation therapy. Also, postoperative complications may delay initiating adjuvant therapy [225].

Neoadjuvant Chemoradiation Therapy
Neoadjuvant chemoradiation therapy is the preferred treatment option for patients with stage II or III disease, although adjuvant chemoradiation therapy remains an acceptable option. Preoperative chemoradiation therapy is the standard of care for patients with clinically staged T3–T4 or node-positive disease (stages II/III) with benefits found in multiple trials, including [222]:

- Tumor regression and downstaging
- Improved tumor resectability
- Higher rates of local control
- Improved toxicity profile of chemoradiation therapy
- Higher rates of sphincter preservation

The most common neoadjuvant regimens for locally advanced tumors of the mid and lower third of the rectum are [225; 226; 227]:

- Short-course radiation therapy with 5 Gy daily for five days, followed by surgery within one week. This approach results in a lower rate of grade 3/4 acute toxicity and better compliance. It is more commonly used when tumor regression and downsizing would not improve resection or sphincter preservation.
- Long-course chemoradiation therapy using 45 to 50.4 Gy over 5 to 6 weeks with concurrent administration of 5-FU, followed by surgery 8 to 12 weeks later. Tumor regression and downsizing is more likely, making sphincter-preserving surgical procedures more feasible.

When followed by proper surgical approach and execution, both regimens provide excellent local control for locally advanced tumors. Combined neoadjuvant radiation therapy and surgery may result in substantial long-term morbidity, including chronic bowel, sphincter, and sexual dysfunction, making careful selection of patients with greatest potential benefit from radiation therapy essential [228; 229]. Neoadjuvant radiation therapy or chemoradiation therapy should not be used in low-risk operable rectal cancer [212].

Adjuvant Therapy
Compared to adjuvant chemoradiation therapy, preoperative chemoradiation therapy is preferred because it decreases local recurrence and adverse effects. However, the evidence demonstrates that compared to observation alone or radiation therapy alone following surgery, adjuvant chemoradiation therapy improves survival and reduces local recurrence rates in patients with resected stage II or III rectal cancer who have not received preoperative radiation therapy [222].

Many patients do not benefit from conventional 5-FU therapy, and introduction of newer chemotherapeutic regimens and biological agents in colon cancer have prompted efforts to enhance survival benefits by optimizing radiation sensitization and chemotherapeutic selection and delivery. The NCCN now recommends FOLFOX or CapeOx (preferred), or FLOX, 5-FU/leucovorin, or capecitabine as adjuvant chemotherapy in stage II/III rectal cancer. This comes with the caveat that conclusive data in rectal cancer are lacking, with recommendation for use in rectal cancer based solely on extrapolation of colon cancer data [198]. The merit of adding oxaliplatin to adjuvant 5-FU/leucovorin in stage II/III rectal cancer is the subject of ongoing debate [230].
Radiotherapy Toxicity
What are potential long-term adverse effects of radiotherapy for rectal cancer?

The greater toxicity concerns with pelvic irradiation of rectal cancer involve potential late-onset morbidity. Relative to patients receiving surgical resection alone, those with additional radiation therapy treatment have shown increased risks of chronic bowel problems, sphincter dysfunction, sexual dysfunction, and elevated risk of surgical morbidity [222].

The improved local tumor control with neoadjuvant radiation therapy should be weighed against greater risks for acute toxicity (e.g., pelvic or perineal wound infection) and chronic/late-onset toxicity (e.g., stool frequency and incontinence problems, pelvic fractures, worsening sexual function). The frequency of these adverse effects found in patients receiving radiation therapy plus surgery versus surgery-only includes fecal incontinence in 62% vs. 38%, and urinary incontinence requiring pad wearing in 56% vs. 33%, respectively [222].

CHEMOTHERAPY AGENTS AND REGIMENS USED IN ADVANCED COLON AND RECTAL CANCER
Which chemotherapeutic agent used in the treatment of advanced colorectal cancer is a novel anti-VEGF molecule that acts as a decoy receptor for VEGF-A and VEGF-B?

Chemotherapy is the primary therapeutic modality for stage IV, metastatic, and recurrent colorectal cancer and the first treatment option for unresectable or metastatic tumors. Metastases develop in at least 50% of colorectal cancer patients, and most metastatic tumors are unresectable. Management of metastatic colorectal cancer involves a continuum of care with sequential use of a variety of active agents in combination or as single agents. The choice of therapy is based on treatment goals, the type and timing of previous therapy, specific efficacy and toxicity profiles, tumor mutational status, and patient preference [231].

The specific chemotherapy agents and combinations used in colon cancer and rectal cancer overlap substantially. The following agents have received FDA approval for use in colorectal cancer [232; 233; 234].

5-Fluorouracil (5-FU)
As discussed, 5-FU has been the foundation of chemotherapy for colorectal cancer for more than four decades. As a single agent, it inhibits tumor cell growth through at least three different mechanisms that ultimately disrupt cellular viability or DNA synthesis, transcription, and replication.

Capecitabine
Capecitabine is an oral fluoropyrimidine that undergoes a three-step enzymatic conversion to 5-FU, with the last step occurring in the tumor cell.

Leucovorin Calcium
Leucovorin is a reduced form of folic acid that does not require enzymatic reduction reaction for activation. This agent allows for purine and pyrimidine synthesis, both of which are needed for normal erythropoiesis. Leucovorin counteracts the toxic effects of current standard combination chemotherapy for colorectal cancer and potentiates the effects of 5-FU and its derivatives by stabilizing the binding of the drug’s metabolite to its target enzyme to prolong drug activity.

Irinotecan Hydrochloride
Irinotecan is inactive in its parent form and is converted by the carboxylesterase enzyme to its active metabolite form SN-38, which is 1,000 times more potent than its parent compound. SN-38 binds to and stabilizes the topoisomerase I-DNA complex and prevents the relegation of DNA after it has been cleaved by topoisomerase I, inhibiting DNA replication. Irinotecan is a current standard therapy for metastatic colon cancer as the combination 5-FU/leucovorin/irinotecan.

Oxaliplatin
A third-generation platinum-based antineoplastic agent, oxaliplatin is used in combination with 5-FU/leucovorin for metastatic colorectal cancer. As with other platinum compounds, oxaliplatin destroys tumor cells through interaction with DNA to form intra-strand/inter-strand DNA cross-linking that interferes with DNA base pairing, replication, and gene transcription, resulting in cell death [235].

Cetuximab
Cetuximab is a partially humanized monoclonal antibody against EGFR that specifically binds to the extracellular domain of EGFRs. The cetuximab-bound EGFR inhibits activation of receptor-associated kinases, which inhibit cell growth, induce apoptosis, and decrease production of matrix metalloproteinase and VEGF. Cetuximab is indicated for the treatment of KRAS mutation-negative (wild-type), EGFR-expressing metastatic colorectal cancer. Importantly, patients with mutant KRAS tumors may experience worse outcome when cetuximab is added to multiagent chemotherapy regimens containing bevacizumab.

Bevacizumab
Bevacizumab is a partially humanized monoclonal antibody that binds to VEGF to inhibit angiogenesis. The inhibition of new blood vessel formation denies blood, oxygen, and other nutrients needed for tumor growth.
<table>
<thead>
<tr>
<th>Name</th>
<th>Agents</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arbeitsgemeinschaft Internistische Onkologie (AIO) or German AIO</td>
<td>Folic acid (leucovorin), 5-FU, and irinotecan</td>
<td>Irinotecan (100 mg/m²) and leucovorin (500 mg/m²) administered as two-hour infusions on day 1, followed by 5-FU (2,000 mg/m²) IV bolus administered via ambulatory pump weekly over 24 hours, four times per year (52 weeks)</td>
</tr>
<tr>
<td>CAPOX</td>
<td>Capecitabine and oxaliplatin</td>
<td>Capecitabine (1,000 mg/m²) twice daily on days 1 through 14, plus oxaliplatin (70 mg/m²) on days 1 and 8 every three weeks</td>
</tr>
<tr>
<td>Douillard</td>
<td>Folic acid (leucovorin), 5-FU, and irinotecan</td>
<td>Irinotecan (180 mg/m²) administered as a two-hour infusion on day 1, leucovorin (200 mg/m²) administered as a two-hour infusion on days 1 and 2, followed by a loading dose of 5-FU (400 mg/m²) IV bolus, then 5-FU (600 mg/m²) administered via ambulatory pump over 22 hours every two weeks on days 1 and 2</td>
</tr>
<tr>
<td>FOLFIRI</td>
<td>Leucovorin, 5-FU, and irinotecan</td>
<td>Irinotecan (180 mg/m²) and leucovorin (400 mg/m²) administered as two-hour infusions on day 1, followed by a loading dose of 5-FU (400 mg/m²) IV bolus administered on day 1, then 5-FU (2,400–3,000 mg/m²) administered via ambulatory pump over 46 hours every two weeks</td>
</tr>
<tr>
<td>FOLFOX4</td>
<td>Oxaliplatin, leucovorin, and 5-FU</td>
<td>Oxaliplatin (85 mg/m²) administered as a two-hour infusion on day 1 and leucovorin (200 mg/m²) administered as a two-hour infusion on days 1 and 2, followed by a loading dose of 5-FU (400 mg/m²) IV bolus, then 5-FU (600 mg/m²) administered via ambulatory pump over 22 hours every two weeks on days 1 and 2</td>
</tr>
<tr>
<td>FOLFOX6</td>
<td>Oxaliplatin, leucovorin, and 5-FU</td>
<td>Oxaliplatin (85–100 mg/m²) and leucovorin (400 mg/m²) administered as two-hour infusions on day 1, followed by a loading dose of 5-FU (400 mg/m²) IV bolus on day 1, then 5-FU (2,400–3,000 mg/m²) administered via ambulatory pump over 46 hours every two weeks</td>
</tr>
<tr>
<td>FUFOX</td>
<td>5-FU, leucovorin, and oxaliplatin</td>
<td>Oxaliplatin (50 mg/m²) plus leucovorin (500 mg/m²) plus 5-FU (2,000 mg/m²) administered as a 22-hour continuous infusion on days 1, 8, 22, and 29 every 36 days</td>
</tr>
<tr>
<td>FUOX</td>
<td>5-FU and oxaliplatin</td>
<td>5-FU (2,250 mg/m²) administered as a continuous infusion over 48 hours on days 1, 8, 15, 22, 29, and 36 plus oxaliplatin (85 mg/m²) on days 1, 15, and 29 every six weeks</td>
</tr>
<tr>
<td>IFL (or Saltz)</td>
<td>Irinotecan, 5-FU, and leucovorin</td>
<td>Irinotecan (125 mg/m²) plus 5-FU (500 mg/m²) IV bolus and leucovorin (20 mg/m²) IV bolus administered weekly for four out of six weeks</td>
</tr>
<tr>
<td>XELOS</td>
<td>Capecitabine plus oxaliplatin</td>
<td>Oral capecitabine (1,000 mg/m²) administered twice daily for 14 days plus oxaliplatin (130 mg/m²) on day 1 every three weeks</td>
</tr>
<tr>
<td>FOLFOXIRI</td>
<td>Irinotecan, oxaliplatin, leucovorin, and 5-FU</td>
<td>Irinotecan (165 mg/m²) administered as a 60-minute infusion, then concomitant infusion of oxaliplatin (85 mg/m²) and leucovorin (200 mg/m²) over 120 minutes, followed by 5-FU (3,200 mg/m²) administered as a 48-hour continuous infusion</td>
</tr>
</tbody>
</table>

Source: [237; 238]

Table 11
Panitumumab
Panitumumab is a fully humanized antibody that binds to EGFR. It is approved by the FDA for use in chemotherapy-refractory metastatic colorectal cancer and is indicated for wild-type KRAS metastatic colorectal cancer.

Ziv-Aflibercept
Ziv-aflibercept is a novel anti-VEGF molecule that acts as a decoy receptor for VEGF-A, VEGF-B, and placental growth factor. The antiangiogenic mechanism of ziv-aflibercept involves competition with VEGF in the blood and extracellular space to prevent VEGF from interacting with its receptors on endothelial cells. It is indicated for metastatic colorectal cancer that is resistant to or has progressed after an oxaliplatin regimen [236].

Regorafenib
Regorafenib inhibits multiple tyrosine kinase pathways, including VEGF, and was approved in 2012 for the treatment of metastatic colorectal cancer in patients previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti-VEGF therapy (e.g., bevacizumab, ziv-aflibercept); and, if KRAS wild type, an anti-EGFR therapy (e.g., cetuximab, panitumumab).

Combination Regimens
The basis of chemotherapy for the treatment of colon and rectal cancer is combination therapy, with agents identified to work synergistically to manage unresectable lesions and minimize drug resistance. These combinations are generally known by their acronyms (Table 11).

RESECTABLE STAGE IV METASTATIC AND RECURRENT COLON AND RECTAL CANCER
With recurrent or advanced colon and rectal cancer, treatment is determined by disease location. For patients with locally recurrent or liver- and/or lung-only metastatic disease, surgical resection, if feasible, is the only potentially curative treatment [180]. At any point, symptom emergence from the primary tumor should become the treatment priority in stage IV colorectal cancer [212].

Stage IV colon cancer denotes distant metastatic disease, and therapeutic options for stage IV recurrent disease include [197]:

- Surgical resection of locally recurrent cancer
- Surgical resection and anastomosis or bypass of obstructing or bleeding primary lesions in selected metastatic cases

- Resection of liver metastases in selected metastatic patients (i.e., those for whom the five-year cure rate for resection of solitary or combination metastases exceeds 20%) or ablation in selected patients
- Resection of isolated pulmonary or ovarian metastases in selected patients
- Palliative radiation therapy
- Palliative chemotherapy
- Targeted therapy
- Clinical trial enrollment

As with colon cancer, surgical resection is the only potentially curative treatment for patients with locally recurrent, liver-only, or lung-only metastatic rectal cancer. Patients with limited pulmonary metastasis and patients with both pulmonary and hepatic metastasis may also be considered for surgical resection, with five-year survival possible in highly selected patients [239; 240]. The presence of hydronephrosis associated with recurrence appears to be a contraindication to surgery with curative intent [241].

Locally recurrent rectal cancer may be resectable, particularly after an inadequate prior operation. For patients with local recurrence alone after an initial attempted curative resection, aggressive local therapy with repeat low anterior resection and coloanal anastomosis, abdominoperineal resection, or posterior or total pelvic exenteration can lead to long-term disease-free survival [165; 242; 243].

The use of induction chemoradiation therapy for previously nonirradiated patients with locally advanced pelvic recurrence (i.e., pelvic side-wall, sacral, and/or adjacent organ involvement) may increase resectability and allow for sphincter preservation [227]. Intraoperative radiation therapy in patients who previously received external-beam radiation therapy may improve local control in patients with locally recurrent disease, with acceptable morbidity [244].

STAGE IV COLORECTAL CANCER WITH UNRESECTABLE OR MEDICALLY INOPERABLE METASTASES
Pivotal studies have established the clinical use and/or FDA approval of chemotherapy and targeted therapy agents and regimens in metastatic colorectal cancer treatment. Unless stated otherwise, all outcomes are median values and all studies were randomized double-blinded with active or placebo control group. Outcomes are time-to-progression, progression-free survival, disease-free survival, and overall survival.
5-FU
When 5-FU was the only available chemotherapeutic option with colorectal cancer activity, trials in patients with locally advanced, unresectable, or metastatic disease showed partial response, prolonged time-to-progression of disease, and improved survival and quality of life compared with best supportive care only. Several trials analyzing the activity and toxicity of various 5-FU/leucovorin regimens found comparable results and median survival of roughly 12 months [245; 246; 247].

Capecitabine
Randomized studies found capecitabine equivalent in efficacy to the 5-FU/leucovorin regimen [248; 249]. Other studies in metastatic colorectal cancer as first-line therapy found non-inferiority between capecitabine/oxaliplatin (CAPOX) and 5-FU/oxaliplatin regimens [250; 251].

Irinotecan and Oxaliplatin
In patients with previously untreated metastatic colorectal cancer, adding irinotecan or oxaliplatin to 5-FU/leucovorin has led to improved treatment response, progression-free survival, and overall survival [252; 253; 254].

A comparison of FOLFOX4 against irinotecan, 5-FU, and leucovorin (IFL) showed progression-free survival of 8.7 vs. 6.9 months and overall survival of 19.5 vs. 15.0 months [255]. Comparisons of FOLFOX and FOLFIRI found identical progression-free survival and overall survival, although patients were allowed to cross over after progression [256; 257].

Patients randomized to FOLFIRI, modified IFL (mIFL), or capecitabine/irinotecan (CAPIRI) showed progression-free survival of 7.6 vs. 5.9 months with FOLFIRI vs. mIFL, and 7.6 vs. 5.8 months with FOLFIRI vs CAPIRI. CAPIRI also led to the highest rates of grade 3 or greater nausea, vomiting, diarrhea, dehydration, and hand-foot syndrome [258].

FOLFOX and FOLFIRI are first-line treatments for patients with metastatic colorectal cancer, with FOLFIRI preferred when using irinotecan [258].

Oxaliplatin
CAPOX was found comparable to 5-FU and oxaliplatin as an oxaliplatin-based regimen for first-line treatment of metastatic colorectal cancer [250; 251]. As second-line treatment following progression on irinotecan and 5-FU/leucovorin, patients randomized to FOLFOX4 or infusional 5-FU/leucovorin showed a median time-to-progression of 4.6 versus 2.7 months [259].

Bevacizumab
Bevacizumab is effective when added to FOLFIRI or FOLFOX as first-line treatment of metastatic colorectal cancer. In a 2009 study of patients with metastatic colorectal cancer, patients randomized to FOLFIRI/bevacizumab showed an overall survival of 28.0 months compared with 19.2 months with mIFL/bevacizumab [260]. In a separate study, patients randomized to IFL/bevacizumab or IFL/placebo showed progression-free survival of 10.6 vs. 6.2 months and overall survival of 20.3 vs. 15.6 months [261].

A trial randomized 1,401 patients with stage IV colorectal cancer to CAPOX or FOLFOX4, and then to bevacizumab or placebo. Patients receiving bevacizumab versus placebo showed progression-free survival of 9.4 vs. 8.0 months and overall survival of 21.3 vs. 19.9 months. Patients in the pooled CAPOX versus FOLFOX4 arms had a progression-free survival of 8.0 vs. 8.5 months. Overall survival had less benefit from bevacizumab than previously reported [262].

In another study, patients who progressed on FOLFIRI were randomized to FOLFOX plus bevacizumab or placebo, and showed a progression-free survival of 7.43 vs. 4.7 months, and overall survival of 12.9 vs. 10.8 months [263]. Based on these studies, bevacizumab was deemed a reasonable addition to FOLFIRI or FOLFOX as first-line treatment of metastatic colorectal cancer.

In a 2012 study, patients progressing on a first-line regimen that included bevacizumab were randomized to a different chemotherapy regimen plus continued bevacizumab or placebo. Participants who continued bevacizumab showed an overall survival of 11.2 months and progression-free survival of 5.7 months, compared with 9.8 months and 4.1 months, respectively, with placebo [124]. These results led to FDA approval of bevacizumab continuation in patients with progression during first-line chemotherapy, allowing patients to continue bevacizumab after switching to a different regimen containing irinotecan or oxaliplatin that may improve the synergistic activity [264].

FOLFOXIRI plus bevacizumab was compared to FOLFIRI plus bevacizumab in patients with untreated metastatic colorectal cancer, who showed a progression-free survival of 12.1 vs. 9.7 months and overall survival of 31.0 vs. 25.8 months. FOLFOXIRI led to significantly more grade 3/4 toxicities, including neutropenia, stomatitis, and peripheral neuropathy [265].
Ziv-Aflibercept
As second-line therapy, 1,226 patients with metastatic colorectal cancer randomized to FOLFIRI plus ziv-aflibercept or placebo showed overall survival of 13.50 vs. 12.06 months and progression-free survival of 6.90 vs. 4.67 months. Both statistically significant outcomes favored ziv-aflibercept, and FOLFIRI plus ziv-aflibercept is an accepted second-line regimen for patients previously treated with FOLFOX [266].

Cetuximab
Tumors with KRAS mutations are cetuximab-insensitive, but adding cetuximab to multiagent chemotherapy improves survival in patients with colorectal cancers lacking KRAS mutation (i.e., KRAS wild type). As discussed, patients with mutant KRAS tumors may experience worse outcomes when cetuximab is combined with bevacizumab. These differences are evident in the clinical trial data.

Patients who progressed on irinotecan regimens randomized to cetuximab plus irinotecan or placebo showed a time-to-progression of 4.2 vs. 1.5 months [267]. A trial of 1,198 patients with stage IV colorectal cancer randomized to FOLFIRI plus cetuximab or placebo found improved progression-free survival but not overall survival with cetuximab. With emerging evidence that cetuximab response is limited to patients with wild-type KRAS tumors, the results were re-analyzed by KRAS status. A significant interactive effect was found for KRAS mutation status and cetuximab treatment response but not progression-free survival, with KRAS wild-type outcomes favoring FOLFIRI and cetuximab [268].

In a 2009 study, patients were randomized to capcitabine/oxaliplatin/bevacizumab plus cetuximab or placebo for metastatic colorectal cancer. The median progression-free survival was 9.4 vs. 10.7 months, and patients with KRAS gene mutation (versus wild-type) receiving cetuximab had progression-free survival of 8.1 vs. 10.5 months. Patients with KRAS tumor mutation receiving cetuximab (as opposed to placebo) showed progression-free survival of 8.1 vs. 12.5 months and overall survival of 17.2 vs. 24.9 months [260].

The benefit of adding cetuximab to first-line combination chemotherapy was studied in patients with KRAS wild-type tumors. The 1,630 patients were randomized into three treatment groups and cetuximab or placebo:

- Arm A: Fluoropyrimidine/oxaliplatin
- Arm B: Fluoropyrimidine/oxaliplatin/cetuximab
- Arm C: Intermittent fluoropyrimidine/oxaliplatin

In patients receiving chemotherapy plus placebo versus cetuximab, the overall survival was 17.9 vs. 17.0 months and progression-free survival was 8.6 vs. 8.6 months. In patients treated continuously (arm A) versus intermittently (arm C), median survival was 15.8 vs. 14.4 months [269; 270]. None of these findings were statistically significant.

In a separate study, patients with EGFR-expressing metastatic colorectal cancer were randomized to first-line FOLFOX-4 plus cetuximab or placebo. The participants did not differ in response rate or progression-free survival. However, in patients with KRAS wild-type tumors, the response rate was 61% vs. 37% and progression-free survival was 7.7 vs. 7.2 months. In contrast, patients with KRAS mutant tumors showed progression-free survival of 5.5 vs. 8.6 months [271].

Panitumumab
Panitumumab is approved for use in patients with chemotherapy-refractory metastatic colorectal cancer. In clinical trials, panitumumab as single agent or combination therapy demonstrated improvements in progression-free survival and overall survival comparable to cetuximab [272; 273; 274].

Regorafenib
The safety and efficacy of regorafenib was evaluated by a single clinical trial of 760 patients with previously treated metastatic colorectal cancer. Participants were randomized to regorafenib or placebo plus best supportive care and showed a median overall survival of 6.4 vs. 5.0 months [275].

Second-Line Chemotherapy
Second-line chemotherapy with irinotecan in patients treated with 5-FU/leucovorin as first-line therapy led to improved overall survival versus infusional 5-FU or supportive care [276]. Conversely, patients who progressed on irinotecan and 5-FU/leucovorin and then received FOLFOX4 or 5-FU/leucovorin showed a median time-to-progression of 4.6 vs. 2.7 months [259].

TREATMENT OF LIVER METASTASES
Approximately 15% to 25% of patients with colorectal cancer will present with liver metastases at diagnosis, and another 25% to 50% will develop metachronous hepatic metastasis after resection of the primary tumor. Only a small proportion of patients with hepatic metastases are candidates for surgical resection, but advances in tumor ablation techniques and regional and systemic chemotherapy administration have now expanded the treatment options [180].
Diagnosis
The diagnostic workup of hepatic metastases should use CT scan to assess hepatic metastases and contrast-enhanced CT of the chest, abdomen, and pelvis to identify extra-hepatic metastases [212]. If intracranial disease is suspected, use of contrast-enhanced MRI of the brain is recommended. If CT shows extra-hepatic metastases potentially amenable to further surgery, a whole-body PET scan may be appropriate. If contrast-enhanced CT suggests pelvic disease, this should be confirmed with pelvic MRI [212].

Surgery
Which factors would make hepatic metastases suitable for resection?
Advances in chemotherapy have steadily improved survival in patients with colorectal cancer liver metastases, with trials now reporting a median survival of 20 months. However, with chemotherapy alone, five-year survival has been poor historically—less than 1%. This has been modestly improved in trials using FOLFOX and/or FOLFOXIRI, with five-year survival rates of 5% to 10% [255; 277]. Despite advances in chemotherapy, liver resection is the best option for achieving long-term survival and may be curative in stage IV disease confined to the liver [278; 279]. Resection of liver metastases with clear margins is associated with a 5-year survival rate of 45% and 10-year overall survival rate of 25% [240; 280; 281; 282].

Hepatic metastases are considered suitable for resection based on the following criteria [180]:

- Limited number of lesions
- Intrahepatic location of lesions
- Lack of major vascular involvement
- Absent or limited extra-hepatic metastases
- Sufficient functional hepatic reserve

Cancer Care Ontario recommends that patients with extra-hepatic metastases limited to the lungs may be suitable for liver resection if all pulmonary metastases are eradicated [280]. Studies of patients with combined liver and lung resection found three-year survival of 36% to 59%, and five-year survival of 9% to 74% [283]. The study showing 74% survival at five years calculated survival from the first metastasectomy instead of the more common second metastasectomy (usually the lungs). Median survival was 42 months when calculated from last metastasectomy [284]. Pooled data from all studies showed five-year survival of 30% [283]. Routine liver resection is not recommended in patients with portal nodal disease or non-pulmonary extra-hepatic metastases [280].

Liver resection is recommended in patients with initially unresectable liver metastases sufficiently downstaged by neoadjuvant chemotherapy. If complete resection has been achieved, adjuvant chemotherapy should be used; neoadjuvant chemotherapy in patients without extra-hepatic metastases led to complete resection in 15% to 36%, and the five-year survival in these patients (33% to 42%) is similar to survival in patients with liver metastases considered resectable without chemotherapy [283]. Consensus is lacking on the best regimen to convert isolated liver metastases from unresectable to resectable [180].

Resection of all lesions, including those with radiographic complete response, is recommended when technically feasible and an adequate functional liver remnant can remain. When a lesion with radiographic complete response is present in an unresectable portion of the liver, surgery may still be an option if all other visible disease can be resected. Adjuvant chemotherapy should also be considered. Closely follow the lesion to allow localized treatment or further resection for in-situ recurrence [280].

Perioperative Chemotherapy
Cancer Care Ontario recommends perioperative chemotherapy for patients with resectable liver metastases and extra-hepatic metastases amenable to resection with clear margins [280]. However, the role of adjuvant chemotherapy in potentially curative liver metastases resection is uncertain. Before FOLFOX and FOLFIRI were introduced, two trials randomized patients after resection of liver metastases to 5-FU/leucovorin or observation. Both studies closed early due to poor accrual, but some data were obtained. Patients randomized to 5-FU/leucovorin or observation had five-year disease-free survival of 33.5% vs. 26.7% and overall survival of 51.1% vs. 41.1% [285]. In patients randomized to post-surgery 5-FU/leucovorin, the progression-free survival was 27.9 months compared with 18.8 months in the observation group [286].

Since the introduction of FOLFOX and FOLFIRI, multi-agent chemotherapy has been evaluated as adjuvant chemotherapy following resection of colorectal cancer liver metastases. In one study, patients randomized to 5-FU/leucovorin or FOLFIRI showed disease-free survival of 21.6 vs. 24.7 months; disease-free survival and overall survival were statistically comparable [287].

In another study, patients with up to four resectable liver metastases received perioperative FOLFOX (six cycles before and after surgery) or surgery alone. The progression-free survival was 42.4% vs. 36.2%. Reversible postoperative complications were more frequent after chemotherapy than surgery alone (25% vs. 16%), and there was one fatality after chemotherapy versus two fatalities after surgery [288].
Based on these findings, some physicians feel perioperative therapy is reasonable [180]. However, improved overall survival from resection plus chemotherapy has not been found.

**Intra-Arterial Chemotherapy After Liver Resection**

Hepatic intra-arterial chemotherapy with fluorouridine for liver metastases has shown higher overall response rates but no consistent improvement in survival compared to systemic chemotherapy. In one trial, patients receiving curative liver resection were randomized to combined hepatic intra-arterial fluorouridine and dexamethasone plus systemic 5-FU/leucovorin or to systemic 5-FU/leucovorin alone. Combined therapy improved two-year progression-free survival (57% vs. 42%) and overall survival (86% vs. 72%) but not median survival (72.2 vs. 59.3 months) [289].

A meta-analysis of randomized trials of fluoropyrimidine systemic therapy found no survival advantage. Furthermore, hepatic intra-arterial therapy is associated with increased local toxic effects, including liver function abnormalities and fatal biliary sclerosis [303].

**Radiofrequency Ablation**

Radiofrequency ablation (RFA) has emerged as a safe technique (2% major morbidity and less than 1% mortality rate) that may provide for long-term tumor control [290]. With RFA, high-frequency alternating current is delivered through needle electrodes inserted into the hepatic tumor area. The generated heat induces localized coagulative necrosis and tissue destruction. RFA is performed under imaging guidance, and the patient receives local or general anesthesia [291].

With hepatic colorectal cancer metastases, RFA is indicated as primary treatment in patients medically unfit for surgery; when the number, location, and size of metastases contraindicate resection; for treatment of post-resection recurrence; and as resection adjunct to ablate small-volume colonies in the future remnant liver. The National Institute for Health and Clinical Excellence (NICE) concluded in 2009 that RFA safety and efficacy evidence was sufficient to support its use in patients unfit or unsuitable for hepatic resection and in patients with previous hepatic resection [291].

**Other Local Ablation**

Cryosurgical ablation is an option for patients with tumors that cannot be resected and for patients who are not candidates for liver resection [292; 293]. Other local ablative techniques include embolization and interstitial radiation therapy [294]. Patients with limited pulmonary metastases, or with both pulmonary and hepatic metastases, may also be considered for surgical resection, with five-year survival possible in select patients [295].

**TREATMENT-INDUCED TOXICITY AND COMPLICATIONS**

**Chemotherapy-Induced Bone Marrow Suppression**

Neutropenia, thrombocytopenia, and anemia may develop with the chemotherapeutic agents used in colorectal cancer treatment. Management of these short-term complications is temporary drug cessation and supportive treatment until recovery of bone marrow function [151].

**Oxaliplatin-Associated Hepatotoxicity**

Elevations in serum liver enzymes are common during treatment with oxaliplatin. Rarely, there is evidence of a hepatic veno-occlusive disease that presents with evidence of portal hypertension or persistent abnormalities in liver biochemistry [151].

**Chemotherapy-Associated Gastrointestinal Toxicity**

Diarrhea, nausea, vomiting, and/or abdominal pain commonly occur with chemotherapeutic agents. Management is symptomatic, with loperamide for diarrhea, antiemetics for nausea and vomiting, and analgesia for pain [151].

**Chemotherapy-Associated Alopecia**

Alopecia is a short-term adverse effect of certain chemotherapies. This effect will resolve with cessation of treatment, but in the interim, management is largely cosmetic.

**Cetuximab-Associated Rash**

Acneiform rash is very common in patients being treated with cetuximab. It primarily occurs on the face and upper torso, often improves with continued treatment, and is reversible. This complication is associated with improved chance of treatment response independent of KRAS status [151].

**Radiation Therapy-Associated Fecal Incontinence**

Loose stool, urgency, and fecal incontinence are common after radiation therapy for rectal cancer [151]. Patients should be prepared for this long-term complication.

**Bladder Dysfunction after Rectal Excision**

Bladder dysfunction can result from damage to the pelvic nerves during rectal cancer surgery. Symptoms can include urinary urgency, incontinence, and retention. Urinary catheterization may be required to relieve retention [151].

**Erectile Dysfunction after Rectal Excision**

Erectile dysfunction can also occur due to pelvic nerve damage. In one study of 28 men treated for colorectal cancer, 24 reported experiencing erectile dysfunction after treatment (i.e., chemotherapy, radiation, and/or surgery) [296]. Almost none of the men in the study received adequate care and education related to this complication.
Oxaliplatin-Associated Pulmonary Fibrosis

Pulmonary fibrosis occurs in less than 1% of patients being treated for colorectal cancer [151]. This generally presents as dry cough, dyspnea, basal crepitations, and pulmonary infiltrates on chest X-ray or CT.

Oxaliplatin-Associated Neuropathy

Neurotoxicity is a common adverse effect of oxaliplatin, usually presenting as acute or chronic peripheral neuropathy. The acute form develops in more than 90% of patients, with usual onset during or shortly after the first few infusions. Symptoms include paresthesias and dysesthesias in the hands, feet, and perioral region, and may be exacerbated by cold. It is self-limiting [151].

The chronic form is a cumulative axonal sensory neuropathy and may be dose limiting. The neuropathy is reversible in most patients after halting treatment. No intervention has shown definitive prevention of neurotoxicity.

Adverse Effects of Anti-EGFR Agents

The adverse effect profile of anti-EGFR agents primarily involves what system?

Anti-EGFR agents have a specific adverse effect profile primarily involving skin toxicities. Electrolyte abnormalities also occur with these agents, especially magnesium-wasting syndrome. Cetuximab is associated with an infusion reaction caused by the immunogenicity of the chimeric antibody. The most prominent adverse effects of anti-EGFR agents are skin lesions (e.g., acneiform eruption, paronychial inflammation) and hair abnormalities (including a marked increase in the length of eyelashes). These are sometimes dose-limiting complications that, while not fatal, can greatly interfere with patients’ quality of life. The development of skin toxicities (particularly more intense reactions) has actually been associated with better outcomes of cetuximab and panitumumab. Preliminary evidence shows benefit with use of a pre-emptive prophylactic skin treatment regimen of skin moisturizers, sunscreen, topical steroids, and doxycycline [194].

POST-TREATMENT FOLLOW-UP

After patients with colorectal cancer finish their treatment, they are often discharged from specialist care, with follow-up performed by community-based family physicians or institution-based, nurse-coordinated care. As there is a transfer of responsibilities, it is important to have guidelines for the follow-up of these patients. A treatment plan from the specialist should be sent to the patient’s other providers, particularly primary care providers, and it should have clear directions on appropriate follow-up [297].

Postoperative surveillance of colorectal cancer is essential, and the objectives are to assess initial treatment efficacy, detect synchronous or metachronous malignancies, and identify potentially curable recurrent or metastatic cancers [298]. The benefits from routine, periodic assessments following colorectal cancer treatment include earlier identification and management of recurrent disease. Clinical trials have shown a significant survival advantage with more intensive follow-up protocols [298; 299].

Several guidelines for surveillance of patients following resection of stage II/III colorectal cancer have been published. Due to minimal available and current data, few surveillance guidelines have been published for patients with stage I or resected metastatic disease [297].

Post-Resection Colon Cancer

Outcomes from several large clinical trials were pooled and analyzed and demonstrated that following resection of the primary tumor, 85% of colon cancer recurrences occur within three years and 95% occur within five years. These results underscored the importance of regular surveillance for a minimum of five years following the resection of stage II and III colon cancer [297]. Accordingly, several professional organizations have published updated practice recommendations for surveillance of patients with resected stage II and III colon cancer. The recommendations by the ASCO, the NCCN, and the joint European Society of Medical Oncology and Japanese Society of Medical Oncology (ESMO/JSMO) are broadly similar but differ on some parameters (Table 12) [297; 300].

Post-Resection Rectal Cancer

Guidelines for surveillance of patients following resection of stage II/III colon and rectal cancer have been produced by Cancer Care Ontario and endorsed by the ASCO. Many recommendations for patients with stage II/III rectal cancer are the same as those described for patients with colon cancer [301]. A medical history, physical examination, and CEA testing should be performed every six months for five years. In addition to abdominal and chest CT imaging, pelvic CT should be performed every 6 to 12 months for two to three years, then annually until five years from surgery.

Rectosigmoidoscopy should be performed every six months for two to five years in patients who did not receive pelvic radiation [301]. In the absence of complete pre-diagnosis colonoscopy, a colonoscopy should be done as soon as is reasonable after completing adjuvant therapy and within six months of completing primary treatment. New and persistent or worsening symptoms, such as pelvic pain, sciatica, and difficulty urinating or defecating, may indicate rectal cancer recurrence.
Carcinoembryonic Antigen

Use of post-treatment CEA testing is usually limited to which patients?

Measurement of the serum glycoprotein CEA as a tumor marker for colorectal cancer has been used to help guide patient management and follow-up. Serum CEA testing is not valuable in screening for colorectal cancer because of its low sensitivity and specificity [302]. Use of postoperative CEA testing is usually limited to patients who may benefit from further intervention, including:

- Patients with stage II or III colorectal cancer
- Patients who would be candidates for resection of liver metastases

Patient Support After Apparently Curative Resection

The NICE recommends offering follow-up to all patients with primary colorectal cancer undergoing treatment with curative intent [203]. Follow-up should begin at an outpatient clinic visit four to six weeks after potentially curative treatment. Regular surveillance with colonoscopy, CEA testing, and CT of the chest, abdomen, and pelvis, should be provided as indicated by the treating oncology team. Any clinical, radiological, or biochemical finding suspicious of recurrent disease should initiate further testing [203]. Regular follow-up may be halted when the patient and healthcare professional have discussed and agreed that likely benefits no longer outweigh risks of further tests or when the patient can no longer tolerate further treatments.

Information About Bowel Function

After any treatment, patients should receive specific information on managing the effects of treatment on their bowel function. This could include information on incontinence, diarrhea, difficulty emptying bowels, bloating, excess flatus, diet, and where to go for help in the event of symptoms. Verbal and written information should be clearly understood by the patient and free from jargon. Information about support organizations or Internet resources may be included.
Culturally and Linguistically Competent Patient Education

As a result of the evolving demographics in the United States, interaction with patients for whom English is not a native language is inevitable. It is each practitioner’s responsibility to ensure that information and instructions are explained in such a way that allows for patient understanding. 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 is being provided, the use of an interpreter should be considered.

CONCLUSION

Several critical needs regarding the care of patients with colorectal cancer have been identified. The high volume of new emerging information on colorectal cancer therapies can overwhelm clinicians who lack the time to adequately review the new information in this rapidly expanding field. However, improved clinician knowledge of the most recent research on new diagnostic and therapy modalities is required in order to improve patient outcomes and reduce side effects.

GLOSSARY

Colostomy: Surgery in which the end of the colon is passed through the abdominal wall to make the stoma [221].

Ileostomy: Surgery whereby the end of the ileum is passed through the abdominal wall to make the stoma [221].

Metachronous colorectal tumors: Primary tumors diagnosed more than six months apart [232].

Oncogene: Mutated form of a gene involved in normal cell growth, which can facilitate cancer cell growth. Gene mutations that become oncogenes arise through an inherited trait or environmental exposure to carcinogens [232].

Ostomy pouch: A removable external collection pouch attached to the stoma and worn outside the body for collection of intestinal contents or stool [221].

Ostomy surgery: Surgery of the bowel (also termed bowel diversion) involving removal of a bowel segment with the need to reroute passage of stool from the anus to and through the abdominal wall [221]. The ostomy brings the end of the intestines through an abdominal incision and attaches it to the skin, creating an opening outside the body.

Stoma: Refers to the end of the intestines that exits through the abdominal incision. Stomas range in width from 0.75–2 inches [221].

Synchronous colorectal tumors: Primary tumors diagnosed within six months of each other [232].

Tumor suppressor gene: Gene that produces a tumor suppressor protein that helps control cell growth. Mutations (changes in DNA) in tumor suppressor genes may promote cancer [232].
Course Availability List

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MODERATE SEDATION/ANALGESIA
#30461 • 15 ANCC / 5 Pharmacology Hours
By Mail – $45 • Online/eBook – $39
Purpose: The purpose of this course is to provide nurses with the knowledge required for safe drug delivery based on standardized operational guidelines. Preprocedural, intraprocedural, and postprocedural patient care are presented, as well as a thorough review of the drugs used, their advantages and disadvantages, and the safe administration of these agents.
Faculty: Susan Engman Lazear, RN, MN
Audience: This course is designed for all nurses, especially those in procedural and diagnostic areas, such as radiology, endoscopy, cardiac cath, out-patient surgery, intensive care, and emergency departments.
Additional Approval: AACN Synergy CERP Category A

ANALGESIC OVERDOSE
#34020 • 5 ANCC / 4 Pharmacology Hours
By Mail – $25 • Online/eBook – $19
Purpose: The purpose of this course is to provide nurses with the information necessary to identify and treat analgesic overdoses in order to prevent unnecessary sequelae.
Faculty: Dana Bartlett, RN, BSN, MSN, MA, CSPI
Audience: This course is designed for nurses who will be caring for patients who have taken an overdose of acetaminophen, aspirin, or ibuprofen.
Additional Approval: AACN Synergy CERP Category A

THYROID DYSDYFUNCTION
#38501 • 4 ANCC / 1 Pharmacology Hour
By Mail – $21 • Online/eBook – $15
Purpose: As a result of the high prevalence of thyroid conditions, nurses and other healthcare providers encounter thyroid dysfunctional patients every day. The purpose of this course is to provide the most current information regarding thyroid disease diagnosis, treatment, and management to facilitate early diagnosis and treatment and optimum patient outcomes.
Faculty: Marilyn Fuller Delong, MA, BSN, RN
Audience: This course is designed for nurses, allied surgical professionals, and other healthcare workers in all practice settings who may care for patients with thyroid dysfunction.
Additional Approval: AACN Synergy CERP Category A

PATHOPHYSIOLOGY: THE CARDIOVASCULAR SYSTEM
#38830 • 15 ANCC / 6 Pharmacology Hours
By Mail – $45 • Online/eBook – $39
Purpose: As health care becomes more complex, it is essential that the theoretical concepts of the basis of illness (pathophysiology) be well understood. The purpose of this course is to reinforce the scientific rationales for the interventions nurses perform and the decisions nurses make as patients move through the ever-changing struggle with their illness.
Faculty: Jane C. Norman, RN, MSN, CNE, PhD
Audience: This course is designed for nurses working in both critical care and coronary care units and those on any medical-surgical unit in which patients with multiple organ system problems are found.
Additional Approval: AACN Synergy CERP Category A

MIGRAINE: DIAGNOSIS AND THERAPEUTIC ADVANCES
#90070 • 5 ANCC / 3 Pharmacology Hours
By Mail – $25 • Online/eBook – $19
Purpose: The purpose of this course are to provide an integrated update of the recent developments on the pathophysiology of migraine and resulting “mechanism-related” therapies, to evaluate the clinical benefit-risk ratio of antimigraine medications, and to summarize the current and evidence-based guidelines for the clinical management of migraine. The information provided should contribute to a more positive interaction between patients and healthcare professionals, through fostering patient awareness, implementation of lifestyle changes, and compliance to therapy.
Faculty: A. José Laüça, MD, PhD
Audience: This course is designed for physicians, physician assistants, nurses, nurse practitioners, and other healthcare professionals involved in the care of patients with known or suspected migraine.
Additional Approval: AACN Synergy CERP Category A

ISCHEMIC STROKE
#90281 • 10 ANCC Hours
By Mail – $35 • Online/eBook – $29
Purpose: The purpose of this course is to provide needed information about the roles of diagnosis and screening, evaluation of individuals with suspected stroke, immediate treatment of stroke, and the elements of effective rehabilitation programs so that healthcare professionals may implement the necessary interventions appropriately.
Faculty: Lori L. Alexander, MTPW, ELS
Audience: This course is designed for physicians, nurses, and physician assistants in the primary care setting. Neurologists and other healthcare practitioners will also benefit from this course.
Additional Approval: AACN Synergy CERP Category A
HIV/AIDS: EPIDEMIC UPDATE FOR WASHINGTON
#94731 • 7 ANCC Hours
By Mail – $25 • Online/eBook – $19
Purpose: In view of the already existing crisis in healthcare in the United States, the problems associated with providing the necessary care for persons with HIV infection or AIDS are significant. The purpose of this course is to address those problems in the discussion of epidemiology, organism characteristics, pathophysiology, transmission, clinical manifestations, complications, treatment advancements, prevention, ethical and legal aspects of care, and workplace concerns.
Faculty: Jane C. Norman, RN, MSN, CNE, PhD; John M. Leonard, MD
Audience: This course is designed for all nurses, physicians, and allied healthcare professionals in Washington involved in the care of patients with HIV/AIDS.
Additional Approval: AACN Synergy CERP Category A

ANTIBIOTICS REVIEW
#95071 • 5 ANCC / 5 PhArm Hours
By Mail – $25 • Online/eBook – $19
Purpose: The purpose of this course is to provide a review of the major classes of antibiotics and their characteristics as well as an overview of selected individual agents within each class that are most useful for today’s clinical practitioner.
Faculty: Donna Coffman, MD
Audience: This course is designed for healthcare providers who prescribe and administer antibiotics to patients, including nurses and nurse practitioners.
Additional Approval: AACN Synergy CERP Category A

MEDICAL MARIJUANA AND OTHER CANNABINOIDS
#95170 • 5 ANCC Hours / 5 PhArm Hours
By Mail – $25 • Online/eBook – $19
Purpose: The purpose of this course is to provide healthcare professionals with unbiased and evidence-based information regarding the use of marijuana and other cannabinoids for the treatment of medical conditions.
Faculty: Mark Rose, BS, MA
Audience: This course is designed for physicians, nurses, and other healthcare professionals working in an adult healthcare setting, where they are likely to encounter patients who are (or should be) receiving medical intervention for control of atrial fibrillation.
Additional Approval: AACN Synergy CERP Category A

PRESCRIPTION OPIOIDS: RISK MANAGEMENT AND STRATEGIES FOR SAFE USE
#91410 • 15 ANCC / 4 PhArm Hours
By Mail – $45 • Online/eBook – $39
Purpose: The purpose of this course is to provide the information necessary for clinicians to make informed decisions regarding prescribed opioids in order to minimize adverse events, substance abuse, and drug diversion.
Faculty: Mark Rose, BS, MA
Audience: This course is designed for physicians, nurses, and physician assistants involved in the care of patients prescribed opioids to treat pain.
Additional Approval: AACN Synergy CERP Category A

CLINICAL MANAGEMENT OF ATRIAL FIBRILLATION
#90821 • 10 ANCC / 4 PhArm Hours
By Mail – $35 • Online/eBook – $29
Purpose: The purpose of this course is to provide a basic review of current treatment options for the management of atrial fibrillation and indications for use, risks, and criteria for evaluating the treatment’s efficacy.
Faculty: Karen Majorowicz, RN, ARNP
Audience: This course is designed for physicians, physician assistants, nurses, and other healthcare professionals working in an adult healthcare setting, where they are likely to encounter patients who are (or should be) receiving medical intervention for control of atrial fibrillation.
Additional Approval: AACN Synergy CERP Category A

CLINICAL CARE OF THE TRANSGENDER PATIENT
#91920 • 10 ANCC / 4 PhArm Hours
By Mail – $35 • Online/eBook – $29
Purpose: The purpose of this course is to provide members of the interdisciplinary healthcare team with the knowledge and resources necessary to improve the care provided to transgender patients, a population historically underserved.
Faculty: Sandra Mesics, CNM, MSN, RN
Audience: This course is designed for all members of the interdisciplinary healthcare team, including physicians, physician assistants, nurses, social workers, therapists, and counselors, involved in the care of transgender patients.
Additional Approval: AACN Synergy CERP Category A

PREDIABETES: AN OPPORTUNITY TO PREVENT DIABETES
#94191 • 15 ANCC / 1 PhArm Hour
By Mail – $45 • Online/eBook – $39
Purpose: Studies have shown that diabetes can be delayed or prevented in people with prediabetes, but risk reduction relies heavily on lifestyle changes on the part of the patients, making education and counseling of vital importance. The purpose of this course is to provide healthcare professionals with the information and skills necessary to effectively deal with this common condition and learn ways to help patients make healthy lifestyle choices.
Faculty: Susan Semb, MSN, RN, CDE
Audience: This course is designed for nurses in adult primary care, clinical, and acute care settings, healthcare and behavioral health professionals in public health and preventive medicine settings, and health education specialists.
Additional Approval: AACN Synergy CERP Category A
FRONTOTEMPORAL DEGENERATION
#96100 • 2 ANCC / 1 PHARM HOUR
By Mail — $16 • Online/eBook — $10
Purpose: The purpose of this course is to provide nurses and other healthcare professionals with current information on frontotemporal degeneration (FTD). Understanding the epidemiology, pathology, clinical features, diagnostic process, genetics, symptom treatment/management, role of brain autopsy, and current research provides a foundation for the care of patients with FTD and support for their families.
Faculty: Ellen Steinbart, RN, MA
Audience: This course is designed for nurses and allied health and mental health professionals who may intervene to support patients with frontotemporal degeneration and their families.
Additional Approval: AACN Synergy CERP Category A

HUMAN TRAFFICKING AND EXPLOITATION
#96311 • 5 ANCC Hours
By Mail — $25 • Online/eBook — $19
Purpose: As human trafficking becomes an increasingly more common problem in the United States, healthcare and mental health professionals will require knowledge of human trafficking patterns, the health and mental health needs of human trafficking victims, and successful interventions for victims. The purpose of this course is to increase the level of awareness and knowledge about human trafficking and exploitation so health and mental health professionals can identify and intervene in cases of exploitation.
Faculty: Alice Yick Flanagan, PhD, MSW
Audience: This course is designed for physicians, nurses, social workers, psychologists, therapists, mental health counselors, and other members of the interdisciplinary team who may intervene in suspected cases of human trafficking and/or exploitation.
Additional Approval: AACN Synergy CERP Category A

DEPRESSION AND SUICIDE
#96401 • 15 ANCC Hours
By Mail — $45 • Online/eBook — $39
Purpose: The purpose of this course is to provide the information and encouragement necessary to allow primary care providers to properly diagnose, treat, and follow-up with patients with depression.
Faculty: Mark Rose, BS, MA
Audience: This course is designed for physicians, nurses, physician assistants, social workers, therapists, and counselors in the primary care setting who may identify and treat depressed and suicidal patients.
Additional Approval: AACN Synergy CERP Category A
Special Approval: This course meets the Washington requirement for 6 hours of Suicide Prevention training.

CHILD ABUSE IDENTIFICATION AND REPORTING: THE NEW YORK REQUIREMENT
#97531 • 2 ANCC Hours
By Mail — $16 • Online/eBook — $10
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.
Faculty: Alice Yick Flanagan, PhD, MSW
Audience: This course is designed for all New York physicians, physician assistants, nurses, social workers, and counselors required to complete child abuse education.
Additional Approval: AACN Synergy CERP Category B
Special Approval: 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
#98641 • 5 ANCC / 1 PHARM HOUR
By Mail — $25 • Online/eBook — $19
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.
Faculty: Lori L. Alexander, MTPW, ELS
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 Approval: AACN Synergy CERP Category B
Special Approval: This course is approved by the New York State Department of Health to fulfill the requirement for 3 hours of Infection Control Training as mandated by Chapter 786 of the Laws of 1992. Provider #TP02078.
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<th>Course #</th>
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</tr>
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<tbody>
<tr>
<td>39020</td>
<td>Geriatric Polypharmacy / 5 Contact Hours</td>
<td>$19</td>
</tr>
<tr>
<td>98881</td>
<td>Sleep Disorders / 10 Contact Hours</td>
<td>$29</td>
</tr>
<tr>
<td>90780</td>
<td>Colorectal Cancer / 15 Contact Hours</td>
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<tr>
<td>30461</td>
<td>Moderate Sedation/Analgesia / 15</td>
<td>$45</td>
</tr>
<tr>
<td>34020</td>
<td>Analgesic Overdose / 5</td>
<td>$25</td>
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<tr>
<td>38501</td>
<td>Thyroid Dysfunction / 4</td>
<td>$21</td>
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<td>38830</td>
<td>Pathophysiology: The Cardiovascular System / 15</td>
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<td>90070</td>
<td>Migraine: Diagnosis and Therapeutic Advances / 5</td>
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<td>Ischemic Stroke / 10</td>
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<td>91410</td>
<td>Prescription Opioids / 15</td>
<td>$45</td>
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<tr>
<td>91920</td>
<td>Clinical Care of the Transgender Patient / 10</td>
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<td>94191</td>
<td>Prediabetes: An Opportunity to Prevent Diabetes / 15</td>
<td>$45</td>
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<tr>
<td>94731</td>
<td>HIV/AIDS: Epidemic Update for Washington / 7</td>
<td>$25</td>
</tr>
<tr>
<td>95071</td>
<td>Antibiotics Review / 5</td>
<td>$25</td>
</tr>
<tr>
<td>95170</td>
<td>Medical Marijuana and Other Cannabinoids / 5</td>
<td>$25</td>
</tr>
<tr>
<td>96100</td>
<td>Frontotemporal Degeneration / 2</td>
<td>$16</td>
</tr>
<tr>
<td>96311</td>
<td>Human Trafficking and Exploitation / 5</td>
<td>$25</td>
</tr>
<tr>
<td>96401</td>
<td>Depression and Suicide / 15</td>
<td>$45</td>
</tr>
<tr>
<td>97531</td>
<td>Child Abuse Identification &amp; Reporting: The NY Req. / 2</td>
<td>$16</td>
</tr>
<tr>
<td>98641</td>
<td>Infection Control: The NY Requirement / 5</td>
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Continuing Education for Nurses ~ Table of Contents ~

- These courses are printed in their entirety on the following pages.
- Course #39020 Geriatric Polypharmacy ................................................................. 1
- Course #98881 Sleep Disorders ............................................................................ 20
- Course #90780 Colorectal Cancer ....................................................................... 52
- Customer Information/Evaluation ..................................................................... Located between pages 88–89
- Course Availability List ........................................................................................ 102–104

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