NetCE

a trchealthcare brand

2023 CONTINUING EDUCATION FOR NEW YORK ADVANCED PRACTICE NURSES

INSIDE THIS EDITION

We Offer Child Abuse, Infection Control, and Pain Management CE (See Course Availability List, page 104).

JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

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

30 Hours
(23 Pharmacology Hrs)
$62

NetCE.com/APRN23

NetCE
a trchealthcare brand

P.O. Box 997571
Sacramento, CA 95899
800-232-4238 | Fax: 916-783-6067

SPECIAL OFFER $62

30 Hours
(23 Pharmacology Hours)
Regular Price $180

Special Offer price of $62 valid through January 31, 2024

After January 31, 2024, price increases to $73

LEARN

Read the enclosed course(s). Study questions will appear throughout the courses to create a link between the learning objectives and the supporting text.

CLICK

Go to **NetCE.com/APRN23**. Enter the Quick Code and Customer ID (found on the back of your booklet), or complete the enclosed forms located between pages 52–53.

DONE

Receive certificates of completion:

FAST
By Mail

FASTER
Fax/Email

FASTEST!
Online
Print from your NetCE transcript.

CONTINUING EDUCATION FOR ADVANCED PRACTICE NURSES 2023

Published by NetCE,
a TRC Healthcare Company
P.O. Box 997571
Sacramento, CA 95899
Tel: 800-232-4238 (within the U.S.)
916-783-4238 (outside the U.S.)
Fax: 916-783-6067
Email: Info@NetCE.com
Website: www.NetCE.com

Opioid Safety: Balancing Benefits and Risks

Includes 5 Pharmacotherapeutic/Pharmacology Hours

This course is designed to meet the requirements for opioid/controlled substance education.

Audience
This course is designed for all nurses, physicians, osteopaths, physician assistants, and pharmacy professionals who may alter prescribing and/or dispensing practices to ensure safe opioid use.

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

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

1. Outline the types of pain and effective approaches to managing different pain types.
2. Describe the Centers for Disease Control and Prevention's most recent guidelines for prescribing opioids.
3. Identify behaviors that are indicative of opioid seeking, diversion, addiction, and/or misuse.
4. Discuss federal and state laws pertaining to the prescription of controlled substances.
5. Create a plan to properly educate patients and families regarding safe opioid use.
6. Describe effects of, potential causes of, and approaches to minimize disparities in pain management.

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

psychiatric/substance use disorders, and acute pharmacologic/toxicologic effects. Mr. Rose is on the Board of Directors of the Minneapolis-based International Institute of Anti-Aging Medicine and is a member of several professional organizations.

Faculty Disclosure

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

Division Planner

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

Director of Development and Academic Affairs

Sarah Campbell

Division Planner/Director Disclosure

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

Accreditations & Approvals

JOINTLY ACCREDITED PROVIDER™ INTERPROFESSIONAL CONTINUING EDUCATION

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

Designations of Credit

NetCE designates this continuing education activity for 5 ANCC contact hours.

IPCE CREDIT™

This activity was planned by and for the healthcare team, and learners will receive 5 Interprofessional Continuing Education (IPCE) credits for learning and change.

NetCE designates this continuing education activity for 5 pharmacotherapeutic/pharmacology contact hours.

AACN Synergy CERP Category A.

Individual State Nursing Approvals

In addition to states that accept ANCC, NetCE is approved as a provider of continuing education in nursing by: Alabama, Provider #ABNP0353 (valid through 07/29/2025); Arkansas, Provider #50-2405; California, BRN Provider #CEP9784; California, LVN Provider #V10662; California, PT Provider #V10842; District of Columbia, Provider #50-2405; Florida, Provider #50-2405; Georgia, Provider #50-2405; Kentucky, Provider #7-0054 (valid through 12/31/2023); South Carolina, Provider #50-2405; West Virginia, RN and APRN Provider #50-2405.

About the Sponsor

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

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

Disclosure Statement

It is the policy of NetCE not to accept commercial support. Furthermore, commercial interests are prohibited from distributing or providing access to this activity to learners.

How to Receive Credit

- Read the following course.
- Complete the Evaluation.
- Return your Customer Information/Evaluation and payment to NetCE by mail or fax, or complete online at **www.NetCE.com/APRN23**.
- A full Works Cited list is available online at www.NetCE.com.

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.

EVIDENCE-BASED PRACTICE RECOMMENDATION

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

INTRODUCTION

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

TYPES OF PAIN AND THE ROLE OF OPIOIDS

ACUTE AND SUBACUTE PAIN

Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute (less than one month) or subacute (one to three months) pain, clinicians should prescribe the lowest effective dose of immediate-release opioids in a quantity no greater than that needed for the expected duration of severe pain [2; 4].

With postoperative, acute, or intermittent pain, analgesia often requires frequent titration, and the two- to four-hour analgesic duration with short-acting hydrocodone, morphine, and oxycodone is more effective than extended-release formulations. Short-acting opioids are also recommended in patients who are medically unstable or with highly variable pain intensity [5; 6; 7].

CHRONIC PAIN

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

interactive activity

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

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

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

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

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

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

EVIDENCE-BASED PRACTICE RECOMMENDATION

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

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

Level of Evidence: Expert Opinion/Consensus Statement

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

PALLIATIVE CARE AND PAIN AT THE END OF LIFE

What administration route is typically preferred for opioids at the end of life as it is the most convenient and least expensive?

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

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

- Fear of addiction to opioids
- Worry that if pain is treated early, there will be no options for treatment of future pain
- Anxiety about unpleasant side effects from pain medications
- Fear that increasing pain means that the disease is getting worse
- Desire to be a "good" patient
- Concern about the high cost of medications

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

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

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

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

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

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

Strong opioids are used for severe pain at the end of life [13; 14]. Morphine, buprenorphine, oxycodone, hydromorphone, fentanyl, and methadone are the most widely used in the United States [19]. Unlike nonopioids, opioids do not have a ceiling effect, and the dose can be titrated until pain is relieved

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

or side effects become unmanageable. Patients who are opioid-naïve or who have been receiving low doses of a weak opioid, the initial dose should be low, and, if pain persists, the dose may be titrated up daily until pain is controlled.

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

CENTERS FOR DISEASE CONTROL AND PREVENTION OPIOID PRESCRIBING GUIDELINE

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

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

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

- Acute, subacute, and chronic pain need to be appropriately and effectively treated independent of whether opioids are part of a treatment regimen.
- Recommendations are voluntary and are intended to support, not supplant, individualized, person-centered care. Flexibility to meet the care needs and the clinical circumstances of a specific patient are paramount.
- A multimodal and multidisciplinary approach to pain management attending to the physical health, behavioral health, long-term services and supports, and expected health outcomes and well-being of each person is critical.

- Special attention should be given to avoid misapplying this updated clinical practice guideline beyond its intended use or implementing policies purportedly derived from it that might lead to unintended consequences for patients.
- Clinicians, practices, health systems, and payers should vigilantly attend to health inequities, provide culturally and linguistically appropriate communication, including communication that is accessible to persons with disabilities, and ensure access to an appropriate, affordable, diversified, coordinated, and effective nonpharmacologic and pharmacologic pain management regimen for all persons.

The following sections are reprinted from the 2022 guideline from the CDC [4].

DETERMINING WHETHER OR NOT TO INITIATE OPIOIDS FOR PAIN

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

Recommendation 1

Nonopioid therapies are at least as effective as opioids for many common types of acute pain. Clinicians should maximize use of nonpharmacologic and nonopioid pharmacologic therapies as appropriate for the specific condition and patient and only consider opioid therapy for acute pain if benefits are anticipated to outweigh risks to the patient. Before prescribing opioid therapy for acute pain, clinicians should discuss with patients the realistic benefits and known risks of opioid therapy (recommendation category: B, evidence type: 3).

Implementation Considerations

Opioids are NOT first-line therapy for which common acute pain conditions?

Nonopioid therapies are at least as effective as opioids for many common acute pain conditions, including low back pain, neck pain, pain related to other musculoskeletal injuries (e.g., sprains, strains, tendonitis, and bursitis), pain related to minor surgeries typically associated with minimal tissue injury and mild postoperative pain (e.g., simple dental extraction), dental pain, kidney stone pain, and headaches including episodic migraine.

Clinicians should maximize use of nonopioid pharmacologic (e.g., topical or oral nonsteroidal anti-inflammatory drugs [NSAIDs], acetaminophen) and nonpharmacologic (e.g., ice, heat, elevation, rest, immobilization, or exercise) therapies as appropriate for the specific condition.

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

Opioids are not first-line therapy for many common acute pain conditions, including low back pain, neck pain, pain related to other musculoskeletal injuries (such as sprains, strains, tendonitis, bursitis), pain related to minor surgeries typically associated with minimal tissue injury and only mild postoperative pain (e.g., dental extraction), dental pain, kidney stone pain, and headaches, including episodic migraine.

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

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

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

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

Recommendation 2

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

Implementation Considerations

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

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

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

Health insurers and health systems can improve pain management and reduce medication use and associated risks by increasing reimbursement for and access to noninvasive, nonpharmacologic therapies with evidence for effectiveness.

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

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

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

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

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

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

In patients with fibromyalgia, tricyclic (amitriptyline) and SNRI antidepressants (duloxetine and milnacipran), NSAIDs (topical diclofenac), and specific anticonvulsants (pregabalin and gabapentin) are used to improve pain, function, and quality of life. Duloxetine, milnacipran, and pregabalin are FDA-approved for the treatment of fibromyalgia. In older adults, decisions to use tricyclic antidepressants should be made judiciously on a case-by-case basis because of risks for confusion and falls.

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

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

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

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

For patients with subacute pain who started opioid therapy for acute pain and have been treated with opioid therapy for ≥30 days, clinicians should ensure that potentially reversible causes of chronic pain are addressed and that opioid prescribing for acute pain does not unintentionally become long-term opioid therapy simply because medications are continued without reassessment. Continuation of opioid therapy at this point might represent initiation of long-term opioid therapy, which should occur only as an intentional decision that benefits are likely to outweigh risks after informed discussion between the clinician and patient and as part of a comprehensive pain management approach.

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

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

Clinicians should review available low-cost options for pain management for all patients, and particularly for patients who have low incomes, do not have health insurance, or have inadequate insurance.

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

OPIOID SELECTION AND DOSAGE

Recommendation 3

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

Implementation Considerations

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

ER/LA opioids should be reserved for severe, continuous pain. The FDA has noted that some ER/LA opioids should be considered only for patients who have received certain dosages of opioids of immediate-release opioids daily for at least 1 week.

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

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

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

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

Recommendation 4

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

Implementation Considerations

The recommendations related to opioid dosages are not intended to be used as an inflexible, rigid standard of care; rather, they are intended to be guideposts to help inform clinician-patient decision-making. Risks of opioid use, including risk for overdose and overdose death, increase continuously with dosage, and there is no single dosage threshold below which risks are eliminated. Therefore, the recommendation language emphasizes that clinicians should avoid increasing dosage above levels likely to yield diminishing returns in benefits relative to risks to patients rather than emphasizing a single specific numeric threshold. Further, these recommendations apply specifically to starting opioids or to increasing opioid dosages, and a different set of benefits and risks applies to reducing opioid dosages (see Recommendation 5).

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

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

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

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

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

to opioid dosages are not intended to be used as an inflexible, rigid standard of care; rather, they are intended to be guideposts to help inform clinician-patient decision-making.

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

Again, the recommendations related to opioid dosages are not intended to be used as an inflexible, rigid standard of care; rather, they are intended to be guideposts to help inform clinician-patient decision making.

Recommendation 5

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

interactive activity

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

Implementation Considerations

Clinicians should carefully weigh both the benefits and risks of continuing opioid medications and the benefits and risks of tapering opioids. If benefits outweigh risks of continued opioid therapy, clinicians should work closely with patients to optimize nonopioid therapies while continuing opioid therapy.

When benefits (including avoiding risks of tapering) do not outweigh risks of continued opioid therapy, clinicians should optimize other therapies and work closely with patients to gradually taper to a reduced opioid dosage or, if warranted based on the individual clinical circumstances of the patient, appropriately taper and discontinue opioid therapy.

In situations where benefits and risks of continuing opioids are considered to be close or unclear, shared decision-making with patients is particularly important.

At times, clinicians and patients might not be able to agree on whether or not tapering is necessary. When patients and clinicians are unable to arrive at a consensus on the assessment of benefits and risks, clinicians should acknowledge this discordance, express empathy, and seek to implement treatment changes in a patient-centered manner while avoiding patient abandonment.

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

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

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

Clinicians should follow up frequently (at least monthly) with patients engaging in opioid tapering. Team members (e.g., nurses, pharmacists, behavioral health professionals) can support the clinician and patient during the ongoing taper process through telephone contact, telehealth visits, or face-to-face visits.

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

Longer duration of previous opioid therapy might require a longer taper. For patients who have taken opioids long-term (e.g., for ≥1 year), tapers can be completed over several months to years depending on the opioid dosage and should be individualized based on patient goals and concerns.

When patients have been taking opioids for longer durations (e.g., for ≥1 year), tapers of 10% per month or slower are likely to be better tolerated than more rapid tapers.

For patients struggling to tolerate a taper, clinicians should maximize nonopioid treatments for pain and should address behavioral distress. Clinically significant opioid withdrawal symptoms can signal the need to further slow the taper rate.

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

Before reversing a taper, clinicians should carefully assess and discuss with the patient the benefits and risks of increasing opioid dosage.

Goals of the taper may vary (e.g., some patients might achieve discontinuation; others might attain a reduced dosage). If the clinician has determined with the patient that the ultimate goal of tapering is discontinuing opioids, after the smallest available dose is reached the interval between doses can be extended and opioids can be stopped when taken less frequently than once a day.

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

Clinicians should advise patients of an increased risk for overdose on abrupt return to a previously prescribed higher dose, because of loss of opioid tolerance, provide opioid overdose education, and offer naloxone.

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

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

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

Clinicians have a responsibility to provide or arrange for coordinated management of patients' pain and opioid-related problems, including opioid use disorder.

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

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

OPIOID DURATION AND FOLLOW-UP

Recommendation 6

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

Implementation Considerations

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

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

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

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

To minimize unintended effects on patients, clinicians, practices, and health systems should have mechanisms in place for the subset of patients who experience severe acute pain that continues longer than the expected duration. These mechanisms should allow for timely re-evaluation to confirm or revise the initial diagnosis and to adjust management accordingly. Clinicians, practices, and health systems can help minimize disparities in access to and affordability of care and refills by ensuring all patients can obtain and afford additional evaluation and treatment, as needed.

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

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

If opioids are continued for ≥1 month, clinicians should ensure that potentially reversible causes of chronic pain are addressed and that opioid prescribing for acute pain does not unintentionally become long-term opioid therapy simply because medications are continued without reassessment.

Continuation of opioid therapy at this point might represent initiation of long-term opioid therapy, which should occur only as an intentional decision that benefits are likely to outweigh risks after discussion between the clinician and patient and as part of a comprehensive pain management approach. Clinicians should refer to recommendations on subacute and chronic pain for initiation (Recommendation 2), follow-up (Recommendation 7), and tapering (Recommendation 5) of ongoing opioid therapy.

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

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

If a taper is needed, taper durations might need to be adjusted depending on the duration of the initial opioid prescription (see supporting rationale for this recommendation for additional details).

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

Recommendation 7

Clinicians should evaluate benefits and risks with patients within one to four weeks of starting opioid therapy for subacute or chronic pain or of dosage escalation. Clinicians should regularly re-evaluate benefits and risks of continued opioid therapy with patients (recommendation category: A, evidence type: 4).

Implementation Considerations

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

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

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

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

Clinicians should follow up with and evaluate patients with subacute pain who started opioid therapy for acute pain and have been treated with opioid therapy for 30 days to reassess the patient's pain, function, and treatment course; ensure that potentially reversible causes of chronic pain are addressed; and prevent unintentional initiation of long-term opioid therapy. Continuation of opioid therapy at this point might represent initiation of long-term opioid therapy, which should occur only as an intentional decision that benefits are likely to outweigh risks after discussion between the clinician and patient and as part of a comprehensive pain management approach (see Recommendation 2).

Clinicians should regularly reassess all patients receiving long-term opioid therapy, including patients who are new to the clinician but on long-term opioid therapy, with a suggested interval of every three months or more frequently for most patients.

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

Clinicians should re-evaluate patients who are at higher risk for opioid use disorder or overdose (e.g., patients with depression or other mental health conditions, a history of substance use disorder, a history of overdose, taking ≥50 MME/day, or taking other central nervous system depressants with opioids) more frequently than every 3 months. Clinicians should regularly screen all patients for these conditions, which can change during the course of treatment (see Recommendation 8).

Clinicians, practices, and health systems can help minimize unintended effects on patients by ensuring all patients can access and afford follow-up evaluation.

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

At follow-up, clinicians should review patient perspectives and goals, determine whether opioids continue to meet treatment goals, including sustained improvement in pain and function and determine whether the patient has experienced common

or serious adverse events or early warning signs of serious adverse events or has signs of opioid use disorder.

Clinicians should ensure that treatment for depression, anxiety, or other psychological comorbidities is optimized.

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

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

ASSESSING RISK AND ADDRESSING HARMS OF OPIOID USE

Recommendation 8

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

Implementation Considerations

Clinicians should ask patients about their drug and alcohol use and use validated tools or consult with behavioral specialists to screen for and assess mental health and substance use disorders.

When considering initiating long-term opioid therapy, clinicians should ensure that treatment for depression and other mental health conditions is optimized, consulting with behavioral health specialists when needed.

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

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

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

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

In part because of concerns about cost of naloxone and access for some patients and reports that purchasing of naloxone has in some cases been required to fill opioid prescriptions, including for patients without a way to afford naloxone, this recommendation specifies that naloxone should be offered to patients. To that end, clinicians, health systems, and payers can work to ensure patients can obtain naloxone, a potentially lifesaving treatment.

Clinicians should avoid prescribing opioids to patients with moderate or severe sleep-disordered breathing when possible to minimize risk for respiratory depression.

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

For pregnant people with opioid use disorder, medication for opioid use disorder (buprenorphine or methadone) is the recommended therapy and should be offered as early as possible in pregnancy to prevent harms to both the patient and the fetus (see Recommendation 12).

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

For patients with jobs that involve potentially hazardous tasks and who are receiving opioids or other medications that can negatively affect sleep, cognition, balance, or coordination, clinicians should assess patients' abilities to safely perform the potentially hazardous tasks (e.g., driving, use of heavy equipment, climbing ladders, working at heights or around moving machinery, or working with high-voltage equipment).

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

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

Although substance use disorder can alter the expected benefits and risks of opioid therapy for pain, patients with co-occurring pain and substance use disorder require ongoing pain management that maximizes benefits relative to risks. (See Recommendation 12 Pain Management for Patients with Opioid Use Disorder for additional considerations specific to these patients.)

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

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

Recommendation 9

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

Implementation Considerations

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

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

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

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

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

Clinicians should take actions to improve patient safety:

- Discuss information from the PDMP with their patient and confirm that their patient is aware of any additional prescriptions. Because clinicians often work as part of teams, prescriptions might appropriately be written by more than one clinician coordinating the patient's care. Occasionally, PDMP information can be incorrect (e.g., if the wrong name or birthdate has been entered, the patient uses a nickname or maiden name, or another person has used the patient's identity to obtain prescriptions).
- Discuss safety concerns, including increased risk for respiratory depression and overdose, with patients found to be receiving overlapping prescription opioids from multiple clinicians who are not coordinating the patient's care or patients who are receiving medications that increase risk when combined with opioids (e.g., benzodiazepines; see Recommendation 11) and offer naloxone (see Recommendation 8).

- Use particular caution when prescribing opioid pain medication and benzodiazepines concurrently, understanding that some patient circumstances warrant prescribing of these medications concomitantly. Clinicians should communicate with others managing the patient to discuss the patient's needs, prioritize patient goals, weigh risks of concurrent benzodiazepine and opioid exposure, and coordinate care (see Recommendation 11).
- Consider the total MME/day for concurrent opioid prescriptions to help assess the patient's overdose risk (see Recommendation 4). Buprenorphine should not be counted in the total MME/day in calculations given its partial agonist properties at opioid receptors that confer a ceiling effect on respiratory depression. If patients are found to be receiving total daily dosages of opioids that put them at risk for overdose, discuss safety concerns with the patient, consider in collaboration with the patient whether or not benefits of tapering outweigh risks of tapering (see Recommendation 5), and offer naloxone (see Recommendation 8).
- Discuss safety concerns with other clinicians who are prescribing controlled substances for their patient. Ideally, clinicians should first discuss concerns with their patient and inform him or her that they plan to coordinate care with the patient's other clinicians to improve the patient's safety.
- Screen for substance use and discuss concerns with their patient in a nonjudgmental manner (see Recommendations 8 and 12).
- When diverting (sharing or selling prescription opioids and not taking them) might be likely, consider toxicology testing to assist in determining whether prescription opioids can be discontinued without causing withdrawal (see Recommendations 5 and 10). A negative toxicology test for prescribed opioids might indicate the patient is not taking prescribed opioids, although clinicians should consider other possible reasons for this test result, such as false negative results or misinterpretation of results (see Recommendation 10).

Recommendation 10

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

Implementation Considerations

Toxicology testing should not be used in a punitive manner but should be used in the context of other clinical information to inform and improve patient care.

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

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

Clinicians, practices, and health systems should aim to minimize bias in testing and should not apply this recommendation differentially based on assumptions about patients.

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

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

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

Limited toxicology screening can be performed with a relatively inexpensive presumptive immunoassay panel that tests for opiates as a class, benzodiazepines as a class, and several nonprescribed substances. Toxicology screening for a class of drugs might not detect all drugs in that class. For example, fentanyl testing is not included in widely used toxicology assays that screen for opiates as a class.

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

- Toxicology results will inform decisions with major clinical or nonclinical implications for the patient
- A need exists to detect specific opioids or other drugs within a class, such as those that are being prescribed, or those that cannot be identified on standard immunoassays
- A need exists to confirm unexpected screening toxicology test results

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

Clinicians might want to discuss unexpected results with the local laboratory or toxicologist and should discuss unexpected results with the patient. Clinicians should discuss unexpected results with patients in a nonjudgmental manner, avoiding use of potentially stigmatizing language (e.g., avoid describing a specimen as testing "clean" or "dirty").

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

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

Recommendation 11

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

Implementation Considerations

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

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

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

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

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

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

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

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

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

Clinicians should communicate with other clinicians managing the patient to discuss the patient's needs, prioritize patient goals, weigh risks of concurrent benzodiazepine and opioid exposure, and coordinate care.

Recommendation 12

Clinicians should offer or arrange treatment evidence-based medications to treat patients with opioid use disorder. Detoxification on its own, without medications for opioid use disorder, is not recommended for opioid use disorder because of increased risks for resuming drug use, overdose, and overdose death (recommendation category: A, evidence type: 1).

Implementation Considerations

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

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

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

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

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

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

For pregnant persons with opioid use disorder, medication for opioid use disorder (buprenorphine or methadone) is the recommended therapy and should be offered as early as possible in pregnancy to prevent harms to both the patient and the fetus.

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

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

Clinicians prescribing opioids should identify treatment resources for opioid use disorder in the community, establish a network of referral options that span the levels of care that patients might need to enable rapid collaboration and referral, when needed, and work together to ensure sufficient treatment capacity for opioid use disorder at the practice level.

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

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

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

Pain Management for Patients with Opioid Use Disorder

Although identification of an opioid use disorder can alter the expected benefits and risks of opioid therapy for pain, patients with co-occurring pain and substance use disorder require ongoing pain management that maximizes benefits relative to risks. Clinicians should use nonpharmacologic and nonopioid pharmacologic pain treatments as appropriate (see Recommendations 1 and 2) to provide optimal pain management [49]. For patients with pain who have an active opioid use disorder but are not in treatment, clinicians should consider buprenorphine or methadone treatment for opioid use disorder, which can also help with concurrent management of pain [49]. For patients who are treated with buprenorphine for opioid use disorder and experience acute pain, clinicians can consider temporarily increasing the buprenorphine dosing frequency (e.g., to twice a day) to help manage pain, given the duration of effects of buprenorphine is shorter for pain than for suppression of withdrawal [49; 50]. For severe acute pain (e.g., from trauma or unplanned major surgery) in patients receiving buprenorphine for opioid use disorder, clinicians can consider additional as-needed doses of buprenorphine. In supervised settings, adding a short-acting full agonist opioid to the patient's regular dosage of buprenorphine can be considered without discontinuing the patient's regular buprenorphine dosage; however, if a decision is made to discontinue buprenorphine to allow for more mu-opioid receptor availability, patients should be monitored closely because high doses of a full agonist opioid might be required, potentially leading to oversedation and respiratory depression as buprenorphine's partial agonist effect lessens. For patients receiving naltrexone for opioid use disorder, and short-term use of higher-potency nonopioid analgesics (e.g., NSAIDs) for patients receiving naltrexone for opioid use disorder. Patients receiving methadone for opioid

use disorder who require additional opioids as treatment for severe acute pain management should be carefully monitored, and when feasible should optimally be treated by a clinician experienced in the treatment of pain in consultation with their opioid treatment program. [49]. The American Society of Addiction Medicine National Practice Guideline for the Treatment of Opioid Use Disorder (2020 Focused Update) provides additional recommendations for the management of patients receiving medications for opioid use disorder who have planned surgeries for which nonopioid therapies are not anticipated to provide sufficient pain relief [49].

RESPONSE TO THE CDC'S OPIOID PRESCRIBING GUIDELINE UPDATE

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

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

IDENTIFICATION OF DRUG DIVERSION/SEEKING BEHAVIORS

Which behaviors are the most suggestive of an emerging opioid use disorder?

Urine drug tests can give insight into patients who are misusing opioids. A random sample of urine drug test results from 800 pain patients treated at a Veterans Affairs facility found that 25.2% were negative for the prescribed opioid while 19.5% were positive for an illicit drug/unreported opioid [22]. Negative urine drug test results for the prescribed opioid do not necessarily indicate diversion but may indicate the patient halted his/her use due to side effects, lack of efficacy, or pain remission. The concern arises over the increasingly stringent climate surrounding clinical decision-making regarding aberrant urine drug test results and that a negative result for the prescribed opioid or a positive urine drug test may serve as the pretense to terminate a patient rather than guide him/her into addiction treatment or an alternative pain management program [23].

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

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

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

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

interactive activity

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

FEDERAL AND STATE LAW

In response to the rising incidence in prescription opioid abuse, addiction, diversion, and overdose since the late 1990s, the FDA has mandated opioid-specific REMS to reduce the potential negative patient and societal effects of prescribed opioids. Other elements of opioid risk mitigation include FDA partnering with other governmental agencies, state professional licensing boards, and societies of healthcare professionals to help improve prescriber knowledge of appropriate and safe opioid prescribing and safe home storage and disposal of unused medication [27].

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

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

CONTROLLED SUBSTANCES LAWS/RULES

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

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

According to the DEA, drugs, substances, and certain chemicals used to make drugs are classified into five distinct categories or schedules depending upon the drug's acceptable medical use and the drug's abuse or dependency potential [30]. The abuse rate is a determinate factor in the scheduling of the drug; for example, Schedule I drugs are considered the most dangerous class of drugs with a high potential for abuse and potentially severe psychologic and/or physical dependence.

STATE-SPECIFIC LAWS AND RULES

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

interactive activity

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

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

PATIENT EDUCATION

What points should be included in the education of patients prescribed opioids?

Patients and caregivers should be counseled regarding the safe use and disposal of opioids. As part of its mandatory Risk Evaluation and Mitigation Strategy (REMS) for extended-release/long-acting opioids, the U.S. Food and Drug Administration (FDA) has developed a patient counseling document with information on the patient's specific medications, instructions for emergency situations and incomplete pain control, and warnings not to share medications or take them unprescribed [11]. A copy of this form may be accessed online at https://www.fda.gov/media/114694/download.

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

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

- Rationale for secure opioid storage
- Warning to protect opioids from theft
- Instructions for disposal of unneeded opioids, based on product-specific disposal information

There are no universal recommendations for the proper disposal of unused opioids, and patients are rarely advised of what to do with unused or expired medications [31]. According to the FDA, most medications that are no longer necessary or have expired should be removed from their containers, mixed with undesirable substances (e.g., cat litter, used coffee grounds), and put into an impermeable, nondescript container (e.g., disposable container with a lid or a sealed bag) before throwing in the trash [32]. Any personal information should be obscured or destroyed. The FDA recommends that certain medications, including oxycodone/acetaminophen (Percocet), oxycodone (OxyContin tablets), and transdermal fentanyl (Duragesic Transdermal System), be flushed down the toilet instead of thrown in the trash [32; 33]. The FDA provides a free toolkit of materials (e.g., social media images, fact sheets, posters) to raise awareness of the serious dangers of keeping unused opioid pain medicines in the home and with information about safe disposal of these medicines. The Remove the Risk Outreach toolkit is updated regularly and can be found at https://www.fda.gov/drugs/ensuring-safe-use-medicine/safe-opioid-disposal-remove-risk-outreach-toolkit [33]. Patients should be advised to flush prescription drugs down the toilet only if the label or accompanying patient information specifically instructs doing so.

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

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

CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

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

DISPARITIES IN PAIN MANAGEMENT

Which of the following strategies can promote positive emotions and help reduce implicit biases?

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

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

Analysis of a national dataset found that Black Americans were less likely to be prescribed opioids for back pain and abdominal pain compared with non-Hispanic White Americans [37]. The authors speculate that racial biases may influence prescribing behaviors. An examination of Medicaid patients who received epidural analgesia during vaginal childbirth also

found statistically significant racial/ethnic differences [38]. In this study, 59.6% of the White patients received epidural analgesia, compared with 49.5% of Black Americans, 48.2% of Asians, and 35.2% of Hispanics. Even after the researchers controlled for age, urban/rural residence, and the availability of anesthesiologists, race and ethnicity still predicted epidural analgesia prescribing trends [38].

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

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

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

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

CONCLUSION

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

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

Customer Information/Evaluation insert located between pages 52–53.

Psychedelic Medicine and Interventional Psychiatry

Includes 8 Pharmacotherapeutic/Pharmacology Hours

Audience

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

Course Objective

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

Learning Objectives

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

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

Faculty

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

Faculty Disclosure

Contributing faculty, Mark S. Gold, MD, DFASAM, DLFAPA, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Division Planner

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

Director of Development and Academic Affairs

Sarah Campbell

Division Planner/Director Disclosure

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

Accreditations & Approvals

JOINTLY ACCREDITED PROVIDER™ INTERPROFESSIONAL CONTINUING EDUCATION

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

NetCE designates this continuing education activity for 10 ANCC contact hours.

IPCE CREDIT™

This activity was planned by and for the healthcare team, and learners will receive 10 Interprofessional Continuing Education (IPCE) credits for learning and change.

NetCE designates this continuing education activity for 8 pharmacotherapeutic/pharmacology contact hours.

AACN Synergy CERP Category A.

Individual State Nursing Approvals

In addition to states that accept ANCC, NetCE is approved as a provider of continuing education in nursing by: Alabama, Provider #ABNP0353 (valid through 07/29/2025); Arkansas, Provider #50-2405; California, BRN Provider #CEP9784; California, LVN Provider #V10662; California, PT Provider #V10842; District of Columbia, Provider #50-2405; Florida, Provider #50-2405; Georgia, Provider #50-2405; Kentucky, Provider #7-0054 (valid through 12/31/2023); South Carolina, Provider #50-2405; West Virginia, RN and APRN Provider #50-2405.

About the Sponsor

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

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

Disclosure Statement

It is the policy of NetCE not to accept commercial support. Furthermore, commercial interests are prohibited from distributing or providing access to this activity to learners.

How to Receive Credit

- Read the following course.
- Complete the Evaluation.
- Return your Customer Information/Evaluation and payment to NetCE by mail or fax, or complete online at **www.NetCE.com/APRN23**.
- A full Works Cited list is available online at www.NetCE.com.

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.

EVIDENCE-BASED PRACTICE RECOMMENDATION

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

What are the categories of psychedelic drugs?

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

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

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

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

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

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

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

Psychedelic drugs are often divided into two categories: classic and non-classic or dissociative. The classic psychedelics are usually derived from naturally occurring compounds and include such drugs as psilocybin, LSD, and DMT, an active component of ayahuasca, an increasingly popular sacramental drink originating from South America. The dissociative psychedelics are typically newer analogs and include ketamine, phencyclidine (PCP), MDMA, mescaline, Salvia divinorum, and dextromethorphan (DXM). While considered drugs of abuse, most agents being tested in psychedelic medicine clinical trials are not self-administered by laboratory animals, the usual test for abuse and dependence liability. If anything, hallucinogens tend to lose their ability to produce changes in the person over time and with regular use. These drugs are all variations on tryptamine, and while they may increase dopamine, they tend to do this through an indirect mechanism.

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

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

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

THE IMPORTANCE OF PSYCHEDELIC AND INTERVENTIONAL MEDICINE

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

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

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

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

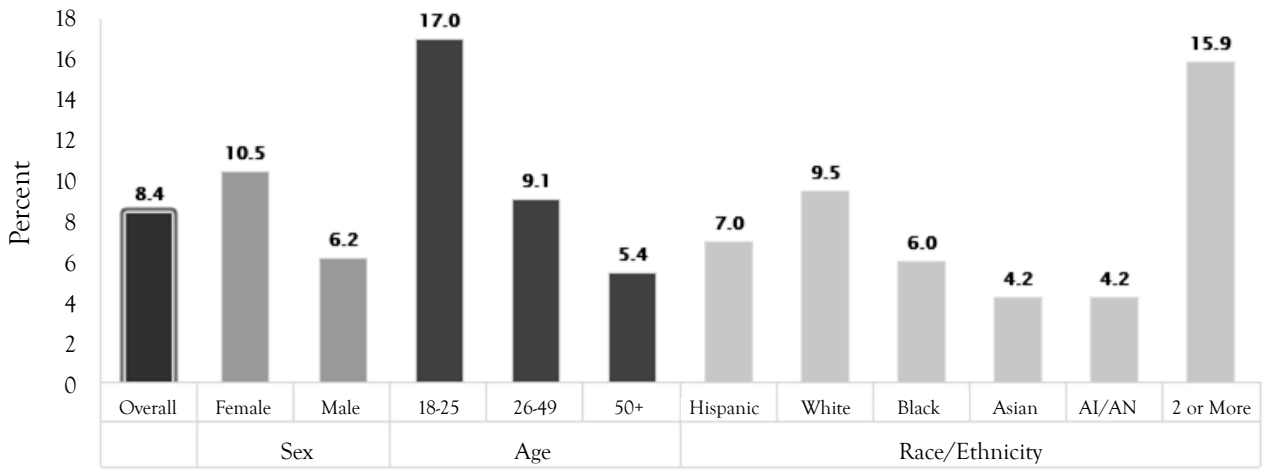
Academic experts, universities, and medical groups continue to research psychedelic medicine, with exciting major breakthroughs in the treatment of depression/anxiety at the end of life and providing relief to patients with treatment-resistant depression, PTSD, and other disorders that most psychiatrists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

TREATMENT-RESISTANT DEPRESSION AND THE RISK OF SUICIDE

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

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

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

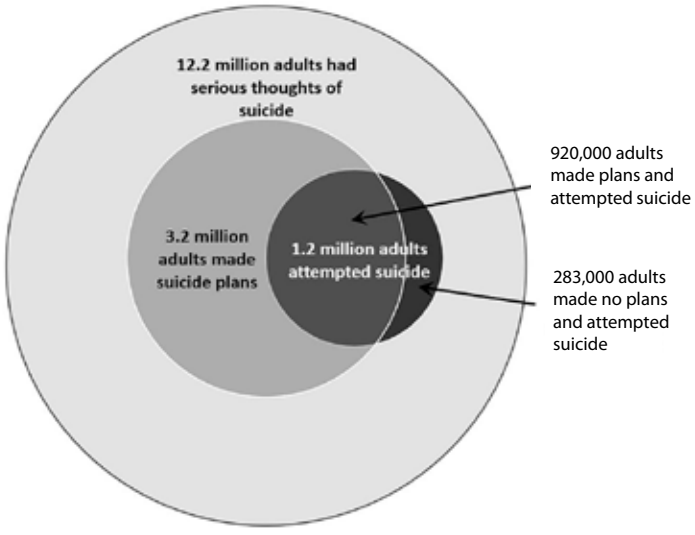


AI/AN = American Indian/Alaska Native

Source: [11]

Figure 1

SUICIDAL BEHAVIORS IN THE UNITED STATES, 2020



Source: [10; 12; 14]

Figure 2

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

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

POOR RESPONSE TO ANTIDEPRESSANTS

When they were first introduced, the monoamine oxide (MAO) inhibitors and tricyclic antidepressants were perceived as wonder drugs for depression. However, MAO inhibitors require strict dietary constraints, and both drug classes are associated with multiple troubling side effects. In contrast, when selective serotonin reuptake inhibitors (SSRIs) were introduced, they were much easier to prescribe and expanded treatment approaches to include primary care. Unfortunately, for many patients, SSRIs did not help as much as expected—or indeed at all, in some cases. Today, it is clear that non- or under-response to pharmacotherapy for major depression is far more common than was realized at the time. For example, researchers have found that antidepressants are ineffective for at least one-third of individuals who take them [2]. Suboptimal responses are also common. Many patients for whom the drugs do not work will recalibrate their expectations and accept the treatment response as the best they can hope to achieve. Treatment discontinuation is common among frustrated patients.

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

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

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

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

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

A GROWING MARKET

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

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

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

CONSUMER INTEREST

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

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

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

PSYCHEDELIC PSYCHIATRY TRAINING PROGRAMS

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

MAPS
https://mapspublicbenefit.com/training

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

Source: Compiled by Author *Table 2*

GROWING BODY OF RESEARCH FROM RESPECTED ACADEMIC AND PHYSICIAN LEADERS

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

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

DEFINITIONS

What is set, in the context of psychedelic medicine?

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

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

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

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

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

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

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

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

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

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

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

PONDERING PSYCHEDELICS

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

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

PSYCHEDELIC DRUG SCHEDULING

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

Source: [23] *Table 3*

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

Another interesting avenue of research has been in the field of addiction medicine. There is some evidence that certain psychedelic drugs, particularly psilocybin, may act as a sort of "anti-gateway drug." Years ago, there was a belief that some (or all) drugs were "gateway drugs," leading inevitably to taking other drugs; for example, this perspective holds that people who smoked marijuana would eventually progress to using "harder" drugs, injecting heroin or other opioids. This theory has largely been discredited and devalued. In fact, several studies have indicated that persons who use hallucinogens are less likely to progress to harder drugs. In one study, researchers used data from nearly 250,000 respondents from the National Survey on Drug Use and Health over the period 2015–2019. Respondents were asked about their past use of classic psychedelics, and these results were then compared to their later abuse (or non-use) of opioids. Individuals who had used psilocybin ("magic mushrooms") in the past had a significantly lower rate (30% lower than average) of opioid misuse and abuse later.

This finding was not replicated with other psychedelic drugs [26]. An earlier study using National Survey on Drug Use and Health data for the period 2008–2013 found that past use of classic psychedelics decreased the risk for past-year opioid dependence by 27% and of opioid abuse by 40% [27].

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

A BRIEF HISTORY OF PSYCHEDELICS

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

Early Days of LSD

In the 1940s, LSD was marketed for the treatment of what conditions?

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

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

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

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

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

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

Early Days of Psilocybin

In 1957, Hofmann received a sample of dried *Psilocybe mexicana* mushrooms from a mycologist in Huautla de Jiménez in Oaxaca, Mexico. The mycologist, R. Gordon Wasson, had received a sample of the mushrooms and information regarding the sacred rituals of the Mazatec people from a curandera to whom he promised secrecy; this promise was obviously not

kept, and Wasson's actions resulted in retaliation against the indigenous woman who he betrayed [138]. Hofmann used paper chromatography to separate the various components of whole extracts of mushrooms and ingested each separated fraction. The active fraction was then chemically characterized, crystallized, and named psilocybin. In 1958, Hofmann and his colleagues subsequently elucidated the structure and synthesis of psilocybin and psilocin, a minor component of the extract that is a dephosphorylated form of psilocybin. In the 1960s, Sandoz Pharmaceuticals began to distribute Indocybin, a psychotherapeutic drug in pill form, containing 2-mg psilocybin. This period also saw research focusing on psilocybin as a probe for brain function and recidivism and as an entheogen used by religious people (divinity students).

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

CONSIDERING PSYCHEDELIC-ASSISTED PSYCHOTHERAPY AS A TREATMENT OPTION

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

LEGAL AND REGULATORY BARRIERS

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

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

Which aspects of a psychedelic medicine setting can enhance set?

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

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

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

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

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

ADVISING PATIENTS CONSIDERING PSYCHEDELIC MEDICINE

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

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

ADDRESSING STIGMA

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

EMERGING PSYCHEDELIC TREATMENTS

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

PSILOCYBIN

In studies using psilocybin, what were the most common adverse reactions?

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

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

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

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

MAJOR PSYCHEDELIC RESEARCH CENTERS IN THE UNITED STATES

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

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

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

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

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

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

Duke University
https://dukepsychedelics.org

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

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

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

Source: Compiled by Author *Table 4*

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

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

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

Another study at Johns Hopkins evaluated the efficacy and safety of psilocybin for the treatment of major depressive disorder. In this randomized study, 24 patients 21 to 75 years of age with moderate-to-severe unipolar depression were randomized to either immediate or delayed treatment.

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

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

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

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

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

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

KETAMINE

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

While ketamine has been used in operative analgesia for decades, it has also become a drug of abuse and misuse [45]. Most notoriously, ketamine became known as a "date-rape drug," because it was administered in drinks to unknowing victims who were subsequently sexually assaulted by their predators. Because ketamine causes amnesia, victims have little or no memory of what occurred to them, although they often experienced after-effects, such as pain. As a result of this growing criminal use, Congress passed the Drug-Induced Rape Prevention and Punishment Act of 1996. During this period and the decade following, there was increased awareness of the dangers of ketamine and other drugs that were used in a similar manner, such as flunitrazepam (Rohypnol) and gamma hydroxybutyric acid (GHB) [46]. As a result, ketamine developed a stigma, and this negative view may persist in many minds.

Ketamine is a Schedule III drug that is a combination of s-ketamine (esketamine) and r-ketamine (arketamine). In 2019, the use of esketamine as a nasal spray (brand name Spravato)

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

EVIDENCE-BASED PRACTICE RECOMMENDATION

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

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

Strength of Recommendation: Weak for

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

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

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

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

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

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

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

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

On day 3, nearly two-thirds (63%) of the patients in the ketamine group achieved full remission from suicidal thoughts. In contrast, 31.6% of the patients in the placebo group were in remission. In nearly 44% of the ketamine subjects, remission occurred within two hours after the first infusion, compared with 7.3% of the placebo group. Ketamine was particularly effective in the bipolar group, while its effect was not significant

in the group with major depressive or other psychiatric disorders. The researchers speculated that ketamine might provide an analgesic kind of effect to mental pain [50].

MDMA

Researchers have demonstrated the efficacy of combination psychotherapy and MDMA in the treatment of what condition(s)?

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

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

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

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

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

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

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

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

group compared with the control group. In the treatment group, 53.2% of subjects reported a PSQI score drop of 3 or more points, compared with 12.5% in the control group [57].

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

IBOGAINE

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

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

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

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

The patient was screened with an electrocardiogram prior to treatment and administered a test dose of ibogaine. During the first four days of treatment, he was administered oxycodone (legally obtained via prescription). The opioid doses were steadily titrated down and on day 4, all opioid medications stopped. During this same period, the patient was given increasing doses of ibogaine. On day 4, the patient was given a "flood dose" of both iboga and ibogaine (variations of the same drug). Between treatments, diazepam was given to support sleep and assuage anxiety. Treatment lasted for six days, and the patient remained at the clinic for a total of eight days. At three-year follow-up, the patient had remained abstinent from opioids, as indicated by negative drug screens. Interestingly, after the flood dose of ibogaine, the client also reported that his chronic pain issues ended, and they have not recurred [62]. The reasons for this finding are unknown.

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

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

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

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

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

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

KRATOM

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

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

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

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

LSD

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

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

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

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

MESCALINE

What are signs of mescaline toxicity?

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

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

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

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

NITROUS OXIDE

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

The anxiolytic action of nitrous oxide is believed to be due to binding at select gamma-aminobutyric acid (GABA) receptors, an action similar to the benzodiazepines [78]. The mild analgesic effect appears to be linked to the endogenous opioid

receptor system, as experimental studies have shown that the introduction of opioid receptor antagonists to the brain decreases the analgesic efficacy of nitrous oxide [79].

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

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

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

The study made it clear that with nitrous oxide, a 25% solution administered over one hour could improve treatment-resistant depression. Most of the study patients had failed an average of 4.5 antidepressants before the study, so the results were significant for a group in need of additional treatment options.

AYAHUASCA/DIMETHYLTRYPTAMINE (DMT)

What is the most common adverse effect of ayahuasca?

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

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

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

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

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

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

DIAGNOSES AND PSYCHEDELIC MEDICINE

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

TREATMENT-RESISTANT DEPRESSION AND SUICIDE

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

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

PTSD

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

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

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

SUBSTANCE USE DISORDERS

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

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

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

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

ANXIETY AND DEPRESSION RELATED TO LIFE-THREATENING DIAGNOSES

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

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

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

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

OBSESSIVE-COMPULSIVE DISORDER

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

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

SOCIAL ANXIETY IN PATIENTS WITH AUTISM

Which psychedelic has been studied for the treatment of social anxiety in persons with autism?

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

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

ANOREXIA NERVOSA

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

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

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

In a 2020 study with only one subject, the researchers treated a patient, 29 years of age, who had developed anorexia nervosa at 14.5 years of age and had been unable to attain remission. The researchers prescribed a ketogenic diet along with intravenous ketamine infusions. (A ketogenic diet was chosen because it had proven in the past to prevent starvation, a real risk with anorexia.) The patient sustained complete recovery and continued her ketogenic diet while maintaining a normal weight [103]. After three months, the woman remained on the ketogenic diet and reported feeling significantly better but still suffered from anorexic compulsions. At that time, she was sent for ketamine infusions. The patient reported that within one hour of her first infusion the "anorexic voice" inside her was decreasing and she felt more like herself. The patient had three more infusions over the next 14 days. After the fourth infusion, the patient stated [103]:

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

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

CLUSTER HEADACHES

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

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

improving a cluster headache condition. There is a current clinical trial underway examining the role of LSD as a possible treatment for cluster headaches [106].

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

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

OTHER DISORDERS

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

INTERVENTIONAL PSYCHIATRY: BRAIN STIMULATION THERAPIES

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

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

ELECTROCONVULSIVE THERAPY

What is the goal of electroconvulsive therapy (ECT)?

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

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

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

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

Level of Evidence: Expert Opinion/Consensus Statement

The modern use of ECT consists of [112]:

> induction of brief general anesthesia (typically lasting less than 10 minutes), pharmacologic muscle relaxation, and continuous monitoring of oxygen saturation, blood pressure, and heart rate, and rhythm. An electrical charge is delivered to the brain through scalp electrodes, which results in a generalized seizure typically lasting for 20 to 60 seconds.

> Most patients receive between 6 and 12 treatments spaced over a period of 2 to 4 weeks as an initial course of treatment.

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

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

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

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

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

TRANSCRANIAL MAGNETIC STIMULATION (TMS)

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

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

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

A Dutch study randomized 14 patients with alcohol use disorder to 10 days of rTMS therapy and 16 patients to sham rTMS. The patients were subsequently evaluated for alcohol craving and alcohol use. For a period of time, subjects in the rTMS

treatment group reported lower levels of alcohol craving and use than those in the control group. Differences in alcohol craving in the study group were most prevalent 3 months after treatment; at the 12-month point, there were no differences between the two groups, indicating the beneficial effects of rTMS may fade over time [122].

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

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

VAGUS NERVE STIMULATION

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

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

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

Some researchers have noted that cognitive dysfunction may accompany depression and be a factor in the associated reduced work productivity. A Canadian study analyzed the cognitive performance of individuals with treatment-resistant depression subsequent to their treatment with VNS. In 14 subjects, both the learning capabilities and memory of the subjects improved significantly after one month of receiving VNS. These cognitive improvements persisted for years subsequent to treatment with VNS. After VNS, 29% of the subjects experienced remission from treatment-resistant depression after 1 month, 50% after 3 months, 57% at 12 months, and 64% at 24 months. As such, at the end of the study, nearly two-thirds of patients had recovered with VNS therapy [128]. The researchers stated [128]:

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

DEEP BRAIN STIMULATION THERAPIES

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

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

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

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

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

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

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

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

CAUTIONS

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

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

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

CONCLUSION

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

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

FACULTY BIOGRAPHY

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

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

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

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

Customer Information/Evaluation insert located between pages 52–53.

Acute Coronary Syndrome: An Overview for Nurses

Includes 10 Pharmacotherapeutic/Pharmacology Hours

Audience

This course is designed for nurses practicing in primary care, inpatient, outpatient, and home care settings to enhance their knowledge of the evidence-based guidelines related to the assessment, management, and secondary prevention of acute coronary syndrome.

Course Objective

The pace at which guidelines for acute coronary syndrome are updated make it challenging for clinicians to remain current with the recommendations that lead to improved outcomes for this substantial patient population. The purpose of this course is to reduce the widening gap between care according to guidelines and actual care delivered by providing nurses with knowledge necessary to implement the most appropriate approach to diagnosis and treatment.

Learning Objectives

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

1. Explain the pathophysiology of ACS, including the role of plaque formation and rupture.
2. Discuss risk factors and key aspects of screening for atherosclerotic plaque and coronary heart disease (CHD).
3. Describe components of triaging patients with suspected ACS.
4. Identify key elements that should be included in the history and physical examination of patients with suspected ACS, including the role of stress tests.
5. List key elements to include in chest pain assessment for a patient with possible ACS.
6. Outline the role of 12-lead ECG and cardiac biomarkers in the diagnosis and risk stratification of ACS.
7. Review key recommendations for the medical and nursing management of patients with UA/NSTEMI, including initial treatment, early inpatient care, and recommended pharmacotherapy.
8. Describe ischemia-guided and invasive strategies related to the management of patients with UA/NSTEMI.
9. Discuss key components of medical and nursing management of patients with variant angina and cocaine-induced ACS.
10. Explain the role of PCI in the management of STEMI, including the issues of timing, stent selection, supporting pharmacologic therapy, risks, and possible complications.
11. Outline the use of fibrinolytic therapy as a reperfusion therapy in the management of STEMI, including the issues of indications, contraindications, supporting pharmacologic therapy, and risks.
12. List key measures used to prevent reocclusion in coronary circulation following reperfusion with PCI or fibrinolytic therapy.
13. Discuss the role of smoking cessation in reducing the risk of recurrent ACS and tools for helping patients quit smoking.
14. Describe other measures patients may take to reduce risk of recurrent ACS and ongoing CHD from hypertension, dyslipidemia, and other modifiable risk factors.
15. Explain factors that impact a patient's adherence to prescribed therapy and measures to reduce risk of recurrent coronary disease.

Faculty

Karen Majorowicz, RN, is currently employed in the Cardiac Intermediate Care Unit at Shands Healthcare at the University of Florida, Gainesville. She received her Master's in Medical-Surgical Nursing in 1978 from the University of Maryland. Karen has created numerous instructional manuals on Medicare and has conducted educational programs on cardiovascular assessment.

Lori L. Alexander, MTPW, ELS, MWC, is President of Editorial Rx, Inc., which provides medical writing and editing services on a wide variety of clinical topics and in a range of media. A medical writer and editor for more than 30 years, Ms. Alexander has written for both professional and lay audiences, with a focus on continuing education materials, medical meeting coverage, and educational resources for patients. She is the Editor Emeritus of the American Medical Writers Association (AMWA) Journal, the peer-review journal representing the

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

Mention of commercial products does not indicate endorsement.

largest association of medical communicators in the United States. Ms. Alexander earned a Master's degree in technical and professional writing, with a concentration in medical writing, at Northeastern University, Boston. She has also earned certification as a life sciences editor and as a medical writer.

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

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

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

Director of Development and Academic Affairs
Sarah Campbell

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

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

Designations of Credit
NetCE designates this continuing education activity for 15 ANCC contact hours.

NetCE designates this continuing education activity for 10 pharmacotherapeutic/pharmacology contact hours.

AACN Synergy CERP Category A.

Individual State Nursing Approvals
In addition to states that accept ANCC, NetCE is approved as a provider of continuing education in nursing by: Alabama, Provider #ABNP0353 (valid through 07/29/2025); Arkansas, Provider #50-2405; California, BRN Provider #CEP9784; California, LVN Provider #V10662; California, PT Provider #V10842; District of Columbia, Provider #50-2405; Florida, Provider #50-2405; Georgia, Provider #50-2405; Kentucky, Provider #7-0054 (valid through 12/31/2023); South Carolina, Provider #50-2405; West Virginia, RN and APRN Provider #50-2405.

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

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

Disclosure Statement
It is the policy of NetCE not to accept commercial support. Furthermore, commercial interests are prohibited from distributing or providing access to this activity to learners.

How to Receive Credit

- Read the following course.
- Complete the Evaluation.
- Return your Customer Information/Evaluation and payment to NetCE by mail or fax, or complete online at **www.NetCE.com/APRN23**.
- A full Works Cited list is available online at www.NetCE.com.

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

Acute coronary syndrome (ACS) is an umbrella term for any condition characterized by symptoms of acute myocardial ischemia caused by an abrupt reduction in blood flow to the heart muscle. Three related but distinct clinical entities fall under the category of ACS: unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI) [1].

Advances in the understanding of the pathophysiology of ACS have led to the identification of UA/NSTEMI and STEMI as distinct clinical entities, with differences in etiology, clinical features, treatment, and outcomes [2; 3; 4]. In addition, the development and evaluation of pharmacologic therapies and reperfusion procedures in a multitude of large-scale trials have resulted in a redefinition of the diagnosis and treatment of acute myocardial infarction (MI). The results of these trials have formed the evidence base for clinical practice guidelines developed by the American College of Cardiology (ACC) and the American Heart Association (AHA), in conjunction with other specialty organizations [2; 3; 5; 6]. Despite the widespread dissemination of these guidelines and documentation of better outcomes and decreased risk for subsequent events with guideline-driven treatment, adherence to many aspects of guideline-directed treatment could be improved [7; 8; 9; 10]. Variations in practice have resulted in reports of disparities in assessment, treatment, and outcomes across subgroups according to age, gender, race/ethnicity, risk level, type of MI, and practice setting [9; 11; 12; 13; 14; 15; 16; 17; 18]. Highlighting the different needs of different populations of patients and the disparities in care, as well as emphasizing the appropriate use of treatment guidelines, can help to reduce the gap between evidence-based care and actual care delivered.

Although physicians are responsible for directing and prescribing care, nurses play a vital role in promoting adherence to practice guidelines. Several quality improvement initiatives developed to help improve adherence to established ACS guidelines have met with success [19]. These initiatives include Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation? (CRUSADE), Guidelines Applied in Practice, and Get With the Guidelines (GWTG) [19; 20; 21]. Studies have indicated that physicians and nurses as well as healthcare systems can improve the quality of care they provide to their patients by implementing a combination of best practices, including participation in continuing education and in quality management efforts [20].

The purpose of this course is to provide nurses practicing in primary care, inpatient, outpatient, or home care settings, as well as those who practice in emergency rooms or in cardiovascular specialty settings, with current information about the evidence-based guidelines for the management of patients with ACS. The program begins with an overview of the scope of the problem and its economic impact on health care in the United States. An overview of the pathophysiology of ACS and its underlying disease process, coronary heart disease (CHD), will be presented to provide background for understanding specific practice recommendations. Clinical signs and symptoms, diagnosis, and management of UA, NSTEMI, and STEMI will be discussed and illustrated through the use of simulated clinical scenarios. Emergent assessment, diagnostic measures, and initial treatment options will be explored, followed by a discussion of follow-up care and preparation for discharge. Key points of secondary prevention, including smoking cessation, treatment of dyslipidemia, and modification of other risk factors, will be outlined.

DEFINITION OF TERMS

Since the early 1990s, an enhanced understanding of the pathogenesis of CHD has helped to create a framework for defining ischemic heart disease. The AHA/ACC define ACS as "a spectrum of conditions compatible with acute myocardial ischemia and/or infarction that are usually due to an abrupt reduction in coronary blood flow" [3]. The concept of ACS is helpful, as the initial clinical presentations of UA, NSTEMI, and STEMI often appear similar. However, UA/NSTEMI and STEMI differ in many ways, including their prevalence, severity, pathophysiology, clinical presentation, treatment, and prognosis.

In patients with CHD, transient imbalances can occur in the supply and demand of oxygen to the myocardium. This ischemia can manifest as precordial chest discomfort, or angina pectoris. Angina is considered stable when it is precipitated by stress or exertion and rapidly resolves with rest or the use of nitrates. Angina is considered unstable when it occurs suddenly (without a precipitating factor); it may occur at rest and may increase in frequency or severity. With both stable angina and UA, ischemia is fully reversible, with no evidence of myocardial necrosis as indicated by elevated levels of serum cardiac biomarkers (e.g., cardiac troponin) [3]. UA may or may not be associated with signs of ischemic changes on electrocardiography (ECG), such as ST-segment depression or new T-wave inversion [3].

UA is closely related to NSTEMI, and the two entities are often indistinguishable from each other, especially during the initial evaluation of a patient [3]. Recognizing the continuum of UA and NSTEMI, the authors of the 2014 AHA/ACC guideline for the management of the conditions created the term NSTE-ACS (non–ST-elevation acute coronary syndromes) to replace "UA/NSTEMI" [3]. Unlike UA, NSTEMI is associated with myocardial necrosis and resultant release of cardiac biomarkers. In addition, the ECG usually shows ST-segment depression, transient ST-elevation, and/or prominent T-wave inversions, but these findings are not required for a diagnosis of NSTEMI [3]. In contrast, STEMI is associated with myocardial damage, with both elevated serum cardiac biomarker levels and persistent ST-segment elevation on ECG [2].

An MI was once defined according to symptoms, ECG abnormalities, and serum cardiac enzyme levels. The advent of more sensitive and specific cardiac biomarkers and imaging studies has led to an ability to detect smaller amounts of myocardial necrosis and, in turn, a need for a more precise definition of MI. The European Society of Cardiology (ESC), the American College of Cardiology Foundation (ACCF), the AHA, and the World Heart Federation jointly developed a consensus document establishing a universal definition of MI, which was most recently updated in 2018 [22]. Among the new concepts introduced, the updated definition differentiates MI from myocardial injury [22]. According to the consensus document, type 1 MI may be diagnosed with the detection of a rise and/or fall of cardiac biomarker levels (preferably high-sensitivity cardiac troponins) with at least one value above the 99th percentile of the upper reference limit (URL) and with at least one of the following [22]:

- Symptoms of acute MI
- New ischemic ECG changes
- Development of pathologic Q waves in the ECG
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology
- Identification of an intracoronary thrombus by angiography or autopsy

Type 2 MI may be diagnosed with the detection of a rise and/or fall of cardiac troponin values with at least one value above the 99th percentile URL, and evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute coronary atherothrombosis, and at least one of the following [22]:

- Symptoms of acute MI
- New ischemic ECG changes
- Development of pathologic Q waves on ECG
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology

Other types are defined as occurring in conjunction with percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), or stent thrombosis; secondary to increased oxygen demand or decreased supply (e.g., coronary artery spasm, arrhythmias); or sudden cardiac death [22]. The consensus document also coins the term MI with nonobstructive coronary arteries (MINOCA) to describe patients with MI and no angiographic obstructive coronary artery disease. The prevalence of MINOCA is estimated to be 6% to 8% among patients diagnosed with MI and appears to be more common in women than men as well as in patients presenting with NSTEMI compared with those presenting with STEMI [22].

SCOPE OF THE PROBLEM

A man presents to the emergency room with complaints of chest pain and shortness of breath. He describes the chest pain as "crushing." When asked to identify the location of the pain, he points to the left substernal area of his chest. He denies previous episodes of chest pain. His initial electrocardiogram (ECG) shows non-specific ST wave changes, and his initial cardiac biomarkers are within normal limits. He is admitted to the cardiology unit with an initial diagnosis of unstable angina.

An elderly man collapses at home. Unable to arouse him, his family calls emergency services. When the paramedics arrive they find him to be in ventricular fibrillation and promptly defibrillate, restoring normal rhythm. An ECG obtained en route shows ST wave changes indicative of an MI. Emergency medical services (EMS) notifies the emergency department that they have a probable ST elevation MI patient en route and call for a STEMI alert.

A young woman presents to the emergency department with complaints of severe chest pain. She is tachycardic with an elevated blood pressure. She has no history of cardiac disease. Her cardiac enzymes are positive for MI, but her 12-lead ECGs show no ST-wave changes. She is admitted to the hospital with diagnosis of NSTEMI.

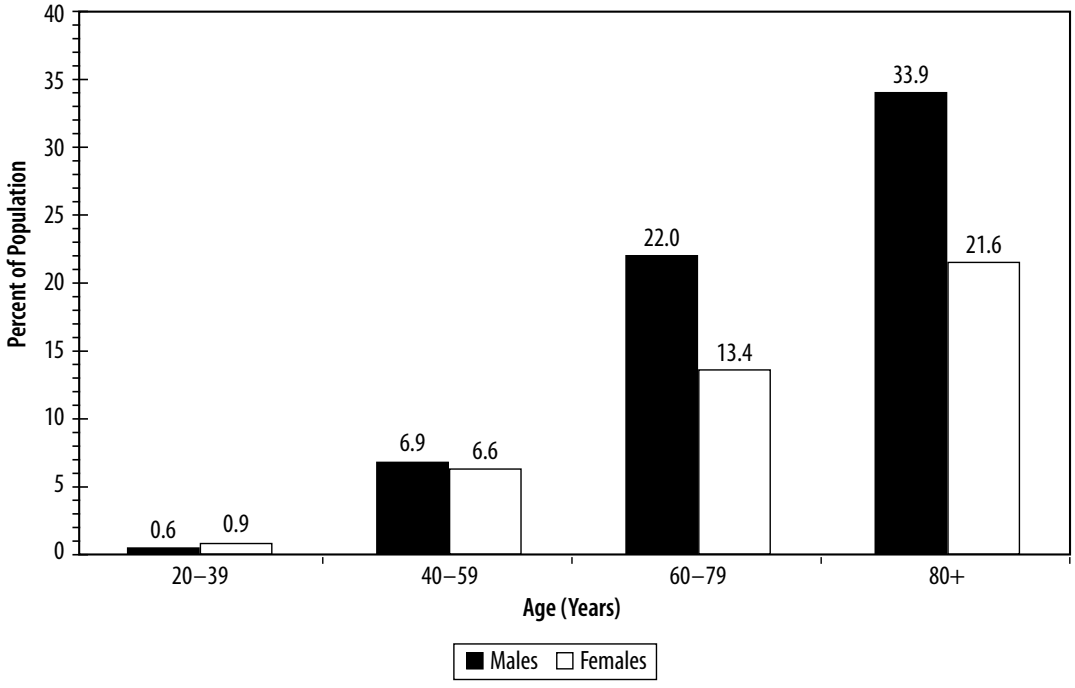
A woman presents to her primary care physician with complaints of increasing episodes of chest pain. Her physician notes that she was diagnosed with stable angina approximately 3 years earlier. Her "typical" angina attack was precipitated by exertion (walking more than five blocks or climbing a flight of stairs). Now, the patient reports that her angina attacks are occurring at rest and occasionally awaken her at night. A 12-lead ECG in the physician's office shows no characteristic ST wave changes. The patient is sent to the local emergency department with a tentative diagnosis of ACS/UA.

Each of these individuals has ACS.

CHD, which encompasses angina pectoris (stable angina), coronary insufficiency (UA), MI, and CHD-related death, affects an estimated 20.1 million Americans 20 years and older in the United States [23]. CHD is the leading cause of death in the United States, accounting for 23.1% of all deaths [24]. It is estimated that each year an estimated 1,055,000 individuals will have a new coronary attack or a recurrent episode [23]. In addition, approximately 170,000 silent first MIs will occur. As a chronic disease, CHD has a significant impact on quality of life, negatively affecting physical, psychologic, and social well-being. CHD also carries a tremendous economic burden: an estimated direct and indirect cost of $219.6 billion [23].

Atherosclerosis, the underlying condition of CHD, is progressive, with periods of stable and nonstable disease. Periods of instability can cause the occurrence of ACS, a spectrum of life-threatening disorders that includes UA, NSTEMI, and STEMI. More than 1 million hospitalizations in 2016 were

PREVALENCE OF MYOCARDIAL INFARCTION BY AGE AND SEX



Source: [23] *Figure 1*

associated with a primary or secondary discharge diagnosis of ACS [23]. As with CHD, the financial cost associated with ACS is high; the mean cost for the first ACS admission is more than $71,300 [23].

PREVALENCE AND MORTALITY OF NSTEMI AND STEMI

The overall prevalence of CHD among adults is 7.2%, with a higher prevalence among men compared with women (8.3% vs. 6.2%) [23]. The prevalence increases with age, with the highest rates found among people 80 years and older (***Figure 1***) [23]. Women tend to be older than men at the time of a first cardiac event [11; 25; 26].

The prevalence of CHD, MI, and angina vary considerably according to gender and race/ethnicity. For CHD, the rate is highest for White men (8.7%) and lowest for Asian women (3.2%). The prevalence of MI is highest for White men (4.4%) and lowest for White and Asian women (2.0% and 0.7%, respectively) (***Table 1***) [23]. The prevalence of angina is highest for Black women (4.7%) and lowest for Asian women (2.2%) [23].

ACS is also more prevalent among men; 615,000 of the more than 1.05 million unique hospitalizations for ACS (as a primary or secondary discharge diagnosis) occurred among men, compared with 430,000 among women [23]. Of all of these unique hospitalizations, 1.02 million were for MI alone, and 23,000 were for UA alone [23]. Data on the population characteristics of patients with MI in the ACTION Registry-GWTG provide insight on racial/ethnic variations in MI. Among 667,424 patients, approximately 86.5% were White, 8.8% were Black, and 2.8% were Asian; 0.7% and 0.3% were American Indian/Alaskan or Hawaiian/Pacific Islander, respectively [28]. In addition, approximately 5.8% were of Hispanic or Latino ethnicity [28].

The incidence of STEMI has decreased since 2003, while the incidence of NSTEMI has increased [2]. STEMI continues to be less prevalent than NSTEMI, accounting for 39% of MIs [23]. However, STEMI is more common than NSTEMI among younger patients, with a rate of nearly 30% among patients younger than 55 years of age and 30% among patients 55 to 64 years of age [28]. STEMI is also more common among some racial/ethnic groups; for example, STEMI accounted for a slightly higher proportion of the MIs among White, Asian, and Hispanic/Latino individuals (***Table 2***) [28].

PREVALENCE OF CORONARY HEART DISEASE (CHD), MYOCARDIAL INFARCTION (MI), AND ANGINA AMONG ADULTS 20 YEARS AND OLDER ACCORDING TO RACE/ETHNICITY								
Condition	**Men**				**Women**			
	White	**Black**	**Hispanic**	**Asian**	**White**	**Black**	**Hispanic**	**Asian**
CHD	8.7%	6.7%	6.8%	5.0%	6.0%	7.2%	6.4%	3.2%
MI	4.4%	3.9%	3.7%	2.7%	2.0%	2.3%	2.1%	0.7%
Angina	4.5%	3.3%	3.5%	2.1%	4.0%	4.7%	4.3%	2.2%
Source: [27]								*Table 1*

PREVALENCE OF NON-ST-ELEVATION MYOCARDIAL INFARCTION (NSTEMI) AND ST-ELEVATION MYOCARDIAL INFARCTION (STEMI) ACCORDING TO RACE/ETHNICITY						
Type of MI	**White**	**Black**	**Asian**	**AI/AN**	**Hawaiian/ PI**	**Hispanic or Latino Ethnicity**
NSTEMI (111,535)	83.4%	13.0%	1.9%	0.9%	0.2%	6.6%
STEMI (71,368)	85.7%	10.1%	2.5%	0.7%	0.2%	6.7%
AI = American Indian, AN = Alaskan Native, PI = Pacific Islander.						
Source: [28]						*Table 2*

As noted, CHD-related mortality rates continue to decrease; the annual rate decreased 27.9% from 2008 to 2018, and the actual number of deaths decreased approximately 9.8% during that time [23]. Heart disease is still the overall leading cause of death in the United States and represents a similar proportion of all deaths for men and women (24.3% vs. 21.8%) [24]. CHD-related mortality varies by age, with CHD accounting for 11.5% of all deaths among people 45 to 54 years of age, approximately 24.5% of all deaths among people 65 to 74 years of age, and approximately 21.5% of all deaths among people 85 years of age and older [24]. CHD-related mortality is higher among men than women across all age groups, except among those 85 years of age and older where the mortality rate is higher among women [24].

With regard to race, CHD is the leading cause of death among all racial/ethnic populations (***Table 3***) [24]. Heart disease is the leading cause of death among non-Hispanic White, non-Hispanic Black, and American Indian/Alaska Native populations, and the second leading cause of death in the non-Hispanic Asian/Pacific Islander and Hispanic populations.

Improved adherence to evidence-based guidelines has been associated with decreased mortality rates after ACS events. Rates of short-term morbidity and mortality are higher for STEMI than for NSTEMI. A review of data in the National Cardiovascular Data Registry ACTION Registry-GTWG showed in-hospital mortality rates of approximately 6% to 8% for STEMI and rates of approximately 0.5% to 5.5% for NSTEMI [28; 29]. The rate of in-hospital cardiogenic shock has also been higher among patients with STEMI (4.4% vs. 1.6%), whereas the rates of in-hospital reinfarction, heart failure, and stroke have been similar (0.8% vs. 0.5%, 4.5% vs. 4.2%, and 0.6% vs. 0.6%, respectively) [28]. At one year, however, the risk of mortality is similar for STEMI and NSTEMI [30].

CORONARY HEART DISEASE (CHD) AS A PERCENTAGE OF ALL DEATHS ACCORDING TO RACE AND ETHNICITY	
Racial/Ethnic Population	**CHD as Percentage of All Deaths**
Race	
White	23.4%
Black	23.5%
Asian	21.2%
American Indian/Alaska Native	17.8%
Native Hawaiian/Other Pacific Islander	24.9%
Ethnicity	
Non-Hispanic White	23.4%
Non-Hispanic Black	23.5%
Hispanic	19.7%
Source: [24]	*Table 3*

PATHOPHYSIOLOGY OF ACS

The underlying cause of ACS is a form of atherosclerosis known as CHD. In CHD, lipids, calcium, fibrin, and other cellular substances/cellular debris are deposited in the lining of the arteries, forming atherosclerotic plaques at sites with low-velocity blood flow (e.g., branch points, inner curvatures) [31]. Although the exact mechanisms are not completely understood, most researchers agree that injury to the inner (endothelial) layer of the artery initiates a series of biochemical events that result in the formation of atherosclerotic plaque. High levels of low-density lipoprotein (LDL) alone can cause atherosclerosis; however, it is most often the case that lower levels of LDL combined with other identified risk factors, including cigarette smoke, low levels of high-density lipoprotein (HDL), hypertension, diabetes, male sex, and family history, lead to atherosclerosis [31]. Individuals with very low LDL typically do not develop clinically significant atherosclerotic plaques, even in the presence of these risk factors.

When the endothelium is injured, an inflammatory response is triggered at the site of the injury. Circulating monocytes respond to the site and become macrophages. These cells act as scavengers, taking up the LDL cholesterol that has penetrated the vessel wall and forming the characteristic foam cell seen in early atherosclerosis. Xanthomas (fatty streaks), the precursors of an atherosclerotic lesion, may be observed in many individuals by 20 years of age. Through complicated mechanisms that include proliferation of smooth muscle cells in the arterial wall and the deposit of extracellular connective tissue, a complex atherosclerotic plaque develops consisting of a fibrous cap overlying a rich lipid core. The fibrous cap may be thick, providing a dense barrier between the circulating blood and the lipid core; this type of lesion is referred to as stable and is less likely to be injured by substances circulating in the blood stream. On some plaques, the fibrous cap is thin and more susceptible to injury; referred to as vulnerable plaque, this type of lesion is more at risk to rupture or erode, causing thrombus formation and disruption of blood flow [1; 32; 33; 34]. Vulnerable plaque has the following hallmark characteristics [31; 35]:

- Large lipid core (more than 40% of the total lesion area)
- Thin, fibrous cap (usually less than 65 micrometers)
- High infiltration of macrophages
- Few smooth muscle cells
- Expansive remodeling preserving the lumen
- Neovascularization from the vasa vasorum
- Adventitial/perivascular inflammation
- Spotty calcification

Growth of plaque narrows the lumen of the affected vessel(s); this disrupts normal blood flow, reduces the blood and oxygen available to the tissue supplied by the vessel, and creates increased turbulent blood flow at the site of the plaque. Initially, the coronary artery responds to the growth of the plaque/narrowing of the vessel lumen through a process of vascular remodeling. In vascular remodeling, the artery enlarges to compensate for the narrowing lumen. However, as the atherosclerotic process continues, the vessel lumen becomes stenosed, unable to dilate or constrict in response to metabolic demands [1; 32; 33; 34].

At one time, it was thought that plaque simply continued to grow larger and larger until the lumen of the affected vessel was totally occluded, disrupting the blood flow and oxygen supply to part of the myocardium. However, today it is acknowledged that the process is much more complex [31; 36; 37]. Research has shown that the precipitating cause of acute myocardial ischemia is not the plaque itself. Instead, acute ischemia occurs when a thrombus forms in the area of plaque, partially or totally occluding the vessel lumen [1; 32; 33; 34].

It should be noted that atherosclerotic plaques are different from xanthomas. Xanthomas are accruals of foam cells that can be seen with the naked eye after several layers have deposited just beneath the endothelium. These fatty streaks are even present in some fetal and infant aortas, due to maternal risk factor influence, but decline in the years after birth. Xanthomas commonly reappear in adolescence in susceptible areas of the arterial tree (e.g., coronary arteries, aorta), and by 20 to 30 years of age, pathologic intimal thickening (formed by isolated lipid pools) is present in many individuals. Not all xanthomas progress, but those at predilection sites may begin to accumulate acellular lipids and cellular debris, forming a necrotic core. These lipid-rich, debris-filled necrotic cores are irreversible. Why some lesions progress to necrosis is not known, but by 30 years of age many more atherosclerotic plaques have developed in men than in women, despite similar numbers of xanthomas in both [31].

PLAQUE RUPTURE AND THROMBUS DEVELOPMENT

Irreversible cardiac tissue death occurs after how many minutes of ischemia?

Formation of a thrombus occurs when the fibrous cap of an atherosclerotic lesion erodes or ruptures, exposing the red cell-rich lipid core to circulating blood. It is thought that the same stimuli that are responsible for the initial injury to the vessel wall are also responsible for causing erosion or rupture of vulnerable plaque (i.e., inflammation). Cigarette smoking and high levels of circulating LDL head the list of injurious agents along with hypertension and diabetes [1; 31; 32; 33; 34].

Plaque rupture generally begins where the cap is thinnest and has the highest infiltration of macrophages, which release lytic enzymes and toxic metabolites that act to degrade the cap, leading to rupture [31]. Plaque rupture triggers the formation of a thrombus when thrombogenic elements of the lipid core are exposed to circulating blood; rupture and thrombosis may occur at the same time, but a temporary increase in stress (emotional or physical) may be the trigger for a cardiac event. However, a life-threatening luminal thrombus develops only occasionally; it is theorized that other factors are involved, such as thrombogenicity of the exposed plaque material, local flow disturbances, and systemic thrombotic propensity [31]. The presence of plaque material interspersed in a thrombus indicates that severe thrombosis developed immediately after plaque rupture; more often, however, the thrombus develops over several days before an ACS event [31]. In one study, the thrombus was days or weeks old in 49% of patients with STEMI [38]. Researchers have used a variety of imaging techniques to determine the distribution of thin-capped fibroatheromas (TCFAs), and the lesions are most often found in the proximal third of the major coronary arteries, although the left circumflex and right coronary arteries were affected evenly throughout their length in one study [39; 40; 41]. The findings of another study suggest that TCFAs causing ACS events are also more likely to be found in proximal locations and that the left main coronary artery was less commonly affected [42].

Why some plaque ruptures cause an ACS event and most do not is unclear. Plaque rupture in nonculprit lesions has been found in approximately 14% of patients with ACS, and among these lesions, plaque burden was significantly greater in lesions with plaque rupture than in lesions without plaque rupture [43]. Plaque rupture in combination with large plaque burden and luminal narrowing appears to lead to ACS [2]. Lipid-rich plaque and intracoronary thrombus have been found significantly less often in patients with asymptomatic CHD compared with patients with NSTEMI [44].

It was once thought that the degree of occlusion caused by a thrombus differentiated STEMI from NSTEMI, with complete and sustained occlusion resulting in STEMI, and incomplete or transient occlusion resulting in NSTEMI [45]. However, research is challenging this theory; for example, studies have shown that the degree of stenosis in some cases of acute MI is not severe enough to limit blood flow [45]. Other studies have demonstrated that ACS is often associated with plaque with little or no calcification and positive vessel remodeling (outward expansion of the artery wall) and that plaque rupture, TCFAs, and red thrombus are significantly more common with STEMI than with NSTEMI [27; 46].

When a thrombus occludes a coronary artery, oxygen supply to the area of the heart supplied by that vessel is reduced. When the supply becomes insufficient to meet the tissue's metabolic demands, the myocardial cells become ischemic; ischemia can develop within 10 seconds. After 1 minute of inadequate oxygen supply, the heart's function is affected. Irreversible tissue death and damage will occur after 20 minutes of ischemia [34].

OTHER CAUSES OF MI

While thrombus formation is the most common cause, several other etiologies may cause ACS. These include cocaine and methamphetamine toxicity and variant angina.

Cocaine/Methamphetamine-Induced ACS

The acute effects of cocaine use include coronary artery vasoconstriction/vasospasm, coronary dissection, thrombus formation, and increased myocardial oxygen demand. Cocaine toxicity creates a setting in which oxygen demand is increased and supply is reduced, leading to ischemia and increased potential for infarction. Patients with cocaine toxicity present with a clinical picture that is almost identical to that of non-cocaine-related ACS. The "typical" patient who presents with cocaine-induced ACS is a male younger than 50 years of age, is a smoker, has used cocaine within several hours before the onset of symptoms, and has few risk factors for CHD. Research has found that long-term effects of cocaine use include the development of premature atherosclerosis, progressive myocyte damage, and hypertrophy of the left ventricle [3; 34; 47; 48].

Methamphetamine can also induce ACS. The acute effects of methamphetamine include arrhythmias, hypertension, and tachycardia, and MI may result from coronary spasm or plaque rupture due to increased platelet aggregation [3]. Chronic methamphetamine use is associated with cardiomyopathy, myocarditis, necrotizing vasculitis, and pulmonary hypertension.

Vasospastic Angina

Also known as variant or Prinzmetal angina, vasospastic angina is caused by vasospasm of the coronary arteries. With vasospasm, the affected artery tightens and narrows. Blood flow through the artery is significantly decreased, reducing the amount of oxygen reaching the tissue. Vasospasm usually occurs spontaneously but may be precipitated by a stress factor such as exercise, hyperventilation, or cold. Smoking increases the risk that a person may develop vasospastic angina. Variant angina may be characterized by transient, intermittent chest pain; the chest pain may occur at rest. With severe spasm that produces almost total occlusion of a vessel, ST-segment elevation may be seen on ECG. This elevation resolves when the spasm is relieved. Variant angina can occur in the absence of atherosclerotic disease but may occur in the area of plaque in persons with CHD [3; 34; 47].

OVERVIEW OF CORONARY CIRCULATION
The vessels that supply the myocardium with oxygen and nutrients are called the coronary arteries. Because these arteries lie on the surface of the myocardium, they are sometimes referred to as epicardial coronary arteries. Two main arteries, known as the right coronary artery and the left coronary artery, emerge from the aorta, very near the top of the heart. The right coronary artery supplies blood to the posterior part of the left ventricle, as well as to the right atrium and right ventricle. Occlusions of the right coronary artery can cause ischemia, injury, or infarction of the right atrium, right ventricle, and the back (or posterior) wall of the left ventricle. The left coronary artery consists of three main segments. Together, the three segments supply a large part of the myocardium with blood. The initial segment arising from the aorta is called the left main coronary (or the left main). The left main coronary quickly branches into two arteries known as the left anterior descending coronary artery and the left circumflex coronary artery. The left anterior descending artery supplies blood to the anterior wall of the left ventricle, the interventricular septum, the right bundle branch, and part of the left bundle branch. The left circumflex circles around the left side of the heart, supplying the lateral wall of the left ventricle, the left atrium, and a posterior part of the left bundle branch. Occlusions of the left main coronary artery are extremely dangerous because obstruction at that level disrupts blood flow through both the left anterior descending artery and the circumflex, causing ischemia, injury, or infarct of a large part of the heart muscle.
Source: [1; 34] *Table 4*

IMPACT ON THE MYOCARDIUM

For the myocardium to conduct electrical impulses, contract, and pump blood effectively, it requires both oxygen and adenosine 5B-triphosphate (ATP) (***Table 4***). When blood flow is interrupted, cells are immediately deprived of their oxygen supply. Anaerobic metabolism of glycogen occurs, and less ATP is produced. Without adequate oxygen and ATP, the sodium-potassium and calcium pumps in the myocardium begin to fail. Hydrogen ions and lactate accumulate, resulting in acidosis. The heart's ability to conduct electrical impulses and to contract becomes impaired. Cardiac output drops, and arrhythmias can develop. If the damage to the myocardium is severe, cardiogenic shock will develop [1].

When the body senses the drop in cardiac output and blood pressure that occur in the acute phase of myocardial ischemia, compensatory mechanisms activate in an attempt to maintain adequate circulation to vital organs. The sympathetic nervous system (SNS) stimulates the release of the hormones epinephrine and norepinephrine; as a result, heart rate and blood pressure increase [1]. Instead of helping the heart compensate for reduced blood flow and oxygen demands, these mechanisms increase myocardial workload and increase myocardial oxygen demands. In addition, the drop in cardiac output triggers the release of renin and angiotensin by the kidney, causing vasoconstriction and retention of sodium and water in an attempt to compensate for reduced output. The amount of blood volume in the ventricles at the end of diastole increases, again increasing myocardial workload and myocardial oxygen demand. Because the oxygen supply to the myocardium is already inadequate, increasing the demands accelerates the ischemic process. Ischemic tissue can become necrotic, resulting in irreversible damage [1]. If more than 40% of the myocardium is damaged, circulatory collapse and cardiogenic shock can result. There is also an increased risk of life-threatening arrhythmias developing during ischemia and infarction [1; 32; 33; 34].

The impact of MI on the heart's ability to maintain adequate cardiac output depends on whether the damage to the myocardium is reversible ischemia or permanent necrosis and the extent and location of the ischemia/infarction [1; 32; 33; 34]. Ischemia causes an immediate impairment of pumping function in the affected tissue; if blood flow is restored, this loss is temporary. If necrosis occurs, the ability of the affected tissue to conduct electrical impulses and contract normally is permanently impaired. In terms of location and extent, factors include the coronary artery or branch involved and where the occlusion is located in the vessel. Lesions in the proximal part of a vessel can result in more damage than lesions in the very distal portion. The part of the heart muscle supplied by the affected artery is also important.

Other complications can occur after acute MI, including pericarditis and left ventricular aneurysm [34]. Pericarditis is inflammation of the pericardial sac surrounding the heart. This condition may develop within days of an infarction, or it may not develop until several weeks later. A common symptom is chest pain that is described as sharp and severe; it often worsens with inspiration and may be relieved when the individual sits up and leans forward. A pericardial friction rub may be auscultated. ST-segment elevations may be seen on 12-lead ECG. Unlike the ST-segment elevations seen in STEMI that occur in the specific leads facing the area of infarct in the heart, in pericarditis, ST segments throughout all 12 leads may be elevated. Nonsteroidal anti-inflammatory drugs (NSAIDs) should not be used to treat pericarditis in the immediate post-infarction period.

When infarction damages the full thickness of the myocardium, the area of damage initially thins. The damaged area loses the ability to conduct electrical impulses or to contract. In the initial period following acute MI, this tissue is very weak and may rupture. As scar tissue forms in the area, the damaged tissue is strengthened but is still unable to conduct electrical impulses or contract. If the area is large enough, an aneurysm can result. This aneurysm is not at risk to rupture, but its presence severely impairs the ability of the left ventricle to contract and maintain cardiac output. Congestive heart failure can result. In some cases, the aneurysm can be surgically resected; removal of the inert, non-contractile tissue has been found to improve overall pumping of the left ventricle. Left ventricular aneurysm formation is associated with infarctions of the anterior and lateral walls of the left ventricular.

RISK FACTORS FOR CHD

Some risk factors for CHD were established many years ago, and researchers continue to seek to identify other risk factors that add predictive value to traditional risk factors.

TRADITIONAL RISK FACTORS

The Framingham Risk Score underestimates CHD risk in which populations?

The Framingham Heart Study identified the first risk factors, and these factors were integrated into a risk-assessment tool, the Framingham Risk Score [49]. The factors in the Framingham Risk Score include age, total cholesterol level, HDL level, systolic blood pressure, treatment for hypertension, and cigarette smoking, and the score is used to determine the 10-year risk of so-called hard CHD (defined as MI or coronary-related death) among asymptomatic adults. The Framingham risk score is one of several scores that involve several traditional risk factors for assessing risk; other scores recommended include the Systematic Coronary Risk Evaluation (SCORE), PROCAM (men) and Reynolds (separate scores for men and women) [50]. The use of one of these risk calculators is a class IB recommendation from the American College of Cardiology Foundation and American Heart Association [50]. It is important to consider the populations on which these risk scores are based. For example, the Framingham Risk Score was developed on the basis of risk factors identified in the Framingham Heart Study, which involved a primarily White, middle-aged population. When the risk score has been evaluated in other populations, it has been found to underestimate the risk of CHD among older (mean age: 73.5 years) Black and White individuals, especially women [51]. ACC/AHA guidelines published in 2013 recommend that race- and sex-specific Pooled Cohort Equations be used to predict 10-year risk of a first hard atherosclerotic cardiovascular disease event in non-Hispanic Black and non-Hispanic White individuals (class IB) [52]. These equations were developed on the basis of data on participants from several large racially and geographically diverse studies [52]. The guidelines also note that the sex-specific pooled cohort equations for non-Hispanic White individuals may be considered to estimate risk for people other than Black and non-Hispanic White individuals (class IB) [52].

Primary care providers are also encouraged to routinely evaluate the presence of individual CHD risk factors, and the U.S. Preventive Services Task Force (USPSTF) has recommended routine screening for hypertension and dyslipidemia as well as counseling and pharmacologic interventions for smoking cessation [53; 54; 55].

NONTRADITIONAL RISK FACTORS

Many nontraditional risk factors have been evaluated for their usefulness in enhancing the estimation of CHD risk, and the ACC/AHA has issued evidence-based recommendations according to individual risk (***Table 5***) [50; 52]. The nontraditional risk factors that have been evaluated most often are inflammatory markers, lipid-related markers, other biochemical markers, testing for subclinical atherosclerosis, ECG, and imaging studies.

Inflammatory Markers

The recognition of the important role of inflammation in the development of CHD has led to increased research on the value of inflammatory markers in predicting risk. C-reactive protein (CRP) is the marker that has been most rigorously studied. The USPSTF found moderate, consistent evidence that adding a CRP level to a risk algorithm improves risk stratification for individuals at intermediate risk, and the 2010 ACCF/AHA guideline subsequently noted that measuring the CRP level may be reasonable for asymptomatic men (50 years of age or younger) or women (60 years of age or younger) who are at intermediate risk for cardiovascular disease [50; 56]. The ACCF/AHA guideline does not recommend a CRP level for asymptomatic adults at high risk [50]. One study suggested improved 10-year risk prediction when a CRP or fibrinogen level was added to a traditional risk score [57]. A later ACCF/AHA guideline notes that a high-sensitivity CRP may be considered when a risk-based treatment decision is uncertain after quantitative risk assessment [52].

The USPSTF found no evidence that homocysteine levels or leukocyte counts were useful in further stratifying risk among individuals at intermediate risk [58].

Lipid-Related Markers

The 2010 ACCF/AHA guideline for assessment of cardiovascular risk does not recommend assessment of lipoprotein or apolipoprotein levels [50]. Measurement of a lipoprotein-associated phospholipase A2 level "might be reasonable" for asymptomatic adults at intermediate risk [50]. In a study published after the ACCF/AHA guideline, the prediction of CHD improved slightly when information on apolipoprotein B and A-I, lipoprotein(a), or lipoprotein-associated phospho-

EVIDENCE-BASED RECOMMENDATIONS FOR USE OF NONTRADITIONAL RISK FACTORS TO EVALUATE CHD RISK IN ASYMPTOMATIC ADULTS	
Nontraditional Risk Factor	**Recommendation (Class, Level of Evidence)**
Family history of CHD	Recommended for all asymptomatic women (IB) May be considered if risk-based treatment decision is uncertain after quantitative risk assessment (IIbB)[a]
Family history of atherothrombotic CHD	Recommended for all asymptomatic adults (IB)
Genomic testing	Not recommended (IIIB)
Lipoprotein and apolipoprotein assessments	Not recommended (IIIC)
Natriuretic peptides	Not recommended (IIIB)
C-reactive protein	May be considered if a risk-based treatment decision is uncertain (after quantitative risk assessment IIbB)[a] Not recommended for asymptomatic adults at high risk (IIIB) May be reasonable for asymptomatic men (50 years of age or younger) or women (60 years of age or younger) who are at intermediate risk (IIbB)
Hemoglobin A1C	May be reasonable for risk assessment in asymptomatic adults who do not have diabetes (IIbB) May be considered for asymptomatic adults with diabetes (IIbB)
Testing for microalbuminuria	Utility is uncertain[a] Reasonable for asymptomatic adults with hypertension or diabetes (IIaB) Might be reasonable for asymptomatic adults at intermediate risk who do not have hypertension or diabetes (IIbB)
Lipoprotein-associated phospholipase A2	Might be reasonable for asymptomatic adults at intermediate risk (IIbB)
Resting electrocardiography (ECG)	Reasonable for asymptomatic adults with hypertension or diabetes (IIaC) May be considered for asymptomatic adults who do not have hypertension or diabetes (IIbC)
Transthoracic echocardiography (to detect left ventricular hypertrophy)	May be considered for asymptomatic adults who have hypertension (IIbB) Not recommended for asymptomatic adults who do not have hypertension (IIIC)
Measurement of carotid intima-media thickness	Not recommended (IIIB)[a] Reasonable for asymptomatic adults at intermediate risk (IIaB)[b]
Brachial/peripheral flow-mediated dilation	Not recommended (IIIB)
Measurement of arterial stiffness	Not recommended outside of research settings (IIIC)
Measurement of ankle-brachial index	May be considered if a risk-based treatment decision is uncertain after quantitative risk assessment (IIbB)[a] Reasonable for asymptomatic adults at intermediate risk (IIaB)
Exercise ECG	May be considered for asymptomatic adults at intermediate risk (IIbB)[c]
Stress echocardiography	Not indicated for asymptomatic adults at low or intermediate risk (IIIC)
Stress myocardial perfusion imaging	Not indicated for asymptomatic adults at low or intermediate risk (IIIC) May be considered for assessment of advanced cardiovascular risk in asymptomatic adults who have diabetes or asymptomatic adults with a strong family history of CHD or when previous risk assessment suggests high risk of CHD (IIbC)

Table 5 continues on next page.

EVIDENCE-BASED RECOMMENDATIONS FOR USE OF NONTRADITIONAL RISK FACTORS TO EVALUATE CHD RISK IN ASYMPTOMATIC ADULTS *(Continued)*	
Nontraditional Risk Factor	**Recommendation (Class, Level of Evidence)**
Coronary artery calcium scoring	May be considered if a risk-based treatment decision is uncertain after quantitative risk assessment(IIbB)[a] Not recommended for persons at low risk (10-year risk <6%) (IIIB) Reasonable for asymptomatic adults at intermediate risk (10-year risk of 10% to 20%) (IIaB) Reasonable for asymptomatic adults (40 years and older) who have diabetes (IIaB) May be reasonable for persons at low to intermediate risk (10-year risk of 6% to 10%) (IIbB)
Coronary computed tomography angiography	Not recommended for asymptomatic adults (IIIC)
Magnetic resonance imaging of plaque	Not recommended for asymptomatic adults (IIIC)
[a]Recommended in the 2014 guideline. [b]Published recommendations on required equipment, technical approach, and operator training and experience for performance of the test must be carefully followed to achieve high-quality results. [c]May also be considered for sedentary adults who plan to start a vigorous exercise program.	
Source: [50; 52]	*Table 5*

lipase A2 mass was added to risk scores that included total cholesterol and HDL levels [59]. However, the 2013 ACCF/AHA guideline notes that the contribution of apolipoprotein B is uncertain [52].

Other Biochemical Markers

According to the 2010 ACCF/AHA guideline, natriuretic peptide levels are not recommended for the evaluation of risk among asymptomatic adults [50]. A hemoglobin A1C "may be reasonable" for assessing risk in asymptomatic adults without diabetes and "may be considered" for asymptomatic adults with diabetes [50]. This guideline also notes that testing for microalbuminuria is reasonable for asymptomatic adults with hypertension or diabetes and "might be reasonable" for asymptomatic adults with hypertension or diabetes who are at intermediate risk [50]. However, in its 2013 guideline, the ACCF/AHA expert panel notes that the contribution of albuminuria is uncertain [52].

Testing for Subclinical Atherosclerosis

Historically, screening for atherosclerosis has been done through measurement of lipid levels as surrogate markers. Now, coronary artery calcium scoring has become a strong risk predictor, improving risk classification of asymptomatic adults when the score is combined with traditional risk factors [60; 61]. The 2010 ACCF/AHA guideline notes that calcium scoring is reasonable for asymptomatic adults at intermediate risk (10-year risk of 10% to 20%), and for asymptomatic adults (40 years and older) who have diabetes and "may be reasonable" for individuals at low-to-intermediate risk (10-year risk of 6% to 10%) [50]. The test is not recommended for persons at low risk (10-year risk of less than 6%). Similarly, 2010 appropriate use criteria state that determination of a coronary calcium score with noncontrast computed tomography (CT) is appropriate for individuals with a family history of premature CHD and for asymptomatic individuals with no known CHD who are at intermediate risk [62]. Subsequent systematic reviews have confirmed that coronary artery calcium scoring has additional predictive value (in combination with traditional risk factors), primarily for asymptomatic individuals at intermediate risk [63; 64]. The 2013 ACCF/AHA guideline notes that a coronary artery calcium (CAC) score may be considered if a risk-based treatment decision is uncertain after quantitative risk assessment [52].

The clinical utility of other tests for identifying subclinical disease is not as clear. In 2009, the USPSTF found no evidence that measurement of carotid intima-media thickness or ankle-brachial index were useful in further stratifying risk among individuals at intermediate risk [58]. However, the 2010 ACCF/AHA guideline notes that measurement of carotid intima-media thickness and ankle-brachial index is reasonable for asymptomatic adults at intermediate risk; however, the 2013 ACCF/AHA guideline does not recommend routine measurement of carotid intima-media thickness and states that ankle-brachial index may be considered if a risk-based treatment decision is uncertain after quantitative risk assessment [50; 52]. The 2010 ACCF/AHA guideline does not recommend measurement of flow-mediated dilation or arterial stiffness as part of risk assessment [50]. Still more recently, systematic reviews have shown that measurement of flow-mediated dilation and carotid intima-media thickness had additional predictive value (in combination with traditional

risk factors), primarily for asymptomatic individuals at intermediate risk [63; 64]. Magnetic resonance imaging of plaque is not recommended [50].

ECG

The ACC/AHA, American College of Physicians (ACP), and USPSTF have all recommended against routine screening with resting ECG and exercise treadmill test for asymptomatic individuals at low risk [50; 64; 65; 66]. The 2010 ACCF/AHA guideline notes that exercise ECG "may be considered" for asymptomatic adults at intermediate risk, but the USPSTF notes that there is insufficient evidence to assess the balance of benefits and harms of such screening among asymptomatic adults at intermediate or high risk [50; 66].

Imaging Studies

The 2010 ACCF/AHA guideline and the ACP screening guideline note that stress echocardiography is not indicated for asymptomatic adults at low or intermediate risk [50; 65]. Transthoracic echocardiography (to detect left ventricular hypertrophy) is not recommended for asymptomatic adults but "may be considered" for asymptomatic adults with hypertension. Coronary CT angiography is not recommended for asymptomatic adults. Stress myocardial perfusion imaging is not indicated for asymptomatic adults at low or intermediate risk but "may be considered" for assessment of advanced cardiovascular risk in asymptomatic adults with diabetes or with a strong family history of CHD [50; 65].

Primary Prevention Interventions Based on Risk Assessment

Primary prevention interventions should be implemented when a patient has one or more risk factors. Recent guideline updates have created shifts away from established goals and thresholds for interventions, especially with regard to hypertension and dyslipidemia.

The 2017 Guideline for High Blood Pressure in Adults sets goals for systolic and diastolic blood pressure and provides evidence-based recommendations on treatment approaches [67]. This guideline replaces the report from the Eighth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC8). One study showed that fewer adults in the United States would need antihypertension treatment according to the JNC8 recommendations, compared with the JNC7 recommendations, while another study indicated that more cardiology patients with hypertension would be treated [68; 69]. The 2017 Guideline for High Blood Pressure in Adults consolidates the recommendations for most major organizations, including the American Society of Hypertension [70]. The authors of a meta-analysis found that, although antihypertension treatment provides similar benefit for individuals at all levels of baseline risk of CHD, the absolute risk reductions are progressively greater as baseline risk increases [71].

With regard to the treatment of cholesterol levels, ACC/AHA guidelines published in 2013 differ greatly from the National Cholesterol Education Program (NCEP) guideline in 2001, with a substantially greater number of people eligible for treatment with cholesterol-lowering drugs, especially within the population of individuals at moderate risk of CHD [72; 73; 74; 75]. The new guideline matches statin assignment to total plaque burden better than the NCEP guideline, according to a study in which plaque burden was determined by CT angiography [76]. A clinician-patient risk discussion is recommended to ensure that patients understand the benefits of risk-reduction interventions, potential adverse effects, drug-drug interactions, and patient preferences [77]. This approach also has the potential to enhance patient adherence to medication.

Increased emphasis has been placed on better management of lifestyle habits as primary prevention of CHD. Lifestyle risk factors such as obesity, poor diet, and physical inactivity have a great influence on traditional risk factors such as blood pressure and cholesterol levels, as well as on novel risk factors, such as inflammation and endothelial function [78]. Lifestyle management is a key component of the new guidelines for the treatment of cholesterol levels and hypertension, and several other guidelines have addressed issues related to lifestyle behaviors, such as obesity, diet, and physical activity. The ACC/AHA/TOS (The Obesity Society) developed a guideline on the management of overweight and obesity, and some members of the Expert Panel authored a separate review on the evidence statements related to cardiovascular risk [79; 80]. The AHA/ACC also published a guideline on lifestyle management to reduce cardiovascular risk in 2013 [81]. In its guideline of cardiac screening, the ACP notes that strategies to improvement lifestyle behaviors should be emphasized [65]. The USPSTF recommends counseling to promote a healthful diet and physical activity to prevent cardiovascular disease, and the AHA focuses on changing lifestyle behaviors in its guide for improving cardiovascular health at the community level [82; 83; 84]. The decision to offer or refer adults without cardiovascular risk factors to behavioral counseling should be individualized by the primary care provider [85].

Another aspect of prevention that warrants increased attention is the role of complementary and alternative medicine. Approximately 33% of adults use complementary and alternative medicine therapy (including dietary supplements), and 40% to 70% do not tell their doctors about the therapy [86; 87; 88]. Systematic reviews have shown that there is insufficient evidence to support the primary prevention of cardiovascular disease with multivitamins, co-enzyme Q10, selenium supplement, green or black tea, or tai chi [89; 90; 91; 92; 93]. Studies have shown that a Mediterranean diet has a beneficial effect on cardiovascular risk factors, although the evidence is limited [94]. The USPSTF recommends against vitamin E supplements and ß-carotene for the prevention of cardiovascular disease [90].

Adherence to guidelines for management of CHD risk and to prevent cardiovascular disease has been suboptimal, especially among patients at low risk for disease [35; 95; 96]. Clinicians have noted several barriers to adhering to CHD prevention guidelines, including [35; 95]:

- Cost of medications
- Lack of reimbursement, especially for lifestyle interventions
- Lack of adequate time for counseling
- Lack of patient education tools
- Existence of multiple guidelines
- Lack of knowledge and skills to recommend dietary changes and facilitate patient adherence

Efforts should be directed at alleviating these barriers to enable healthcare professionals to evaluate patients' risk factors adequately and to develop ways to help patients understand their risk and the importance of prevention strategies. A multidisciplinary team approach is needed to provide expertise in all areas. In addition, initiatives should emphasize the risk of CHD among women.

TRIAGE

What is a primary goal of the initial evaluation of a patient with suspected ACS?

Use of EMS transport is associated with substantial decreases in ischemia time and in treatment delays [97]. Unfortunately, studies have shown that 40% to 80% of patients with ACS symptoms do not use emergency medical services, with high rates of self-transport among minority populations [97; 98; 99]. If a person is not at a healthcare facility when he or she develops signs of ACS, the following actions should be taken:

- 911 should be called to transport the patient to the hospital via emergency medical services. Friends or family should not drive the patient to the hospital.
- Persons out of the hospital setting who develop symptoms of ACS and who already have a prescription for sublingual nitroglycerin should take no more than 1 dose of nitroglycerin. If chest pain is not relieved within 5 minutes, the person should call emergency medical services before taking any more nitroglycerin.
- During transport to the hospital, emergency medical services should give the patient 162–325 mg of aspirin (chewed or crushed, not swallowed whole).

When a patient presents with clinical signs suspicious for MI, immediate medical intervention is directed at confirming a diagnosis and stratifying the person's risk for adverse events such as cardiac arrest and severe/significant damage to the myocardium [3]. It is imperative to quickly identify patients with chest pain and other symptoms suggestive of ACS, and registration staff and triage nurses should be familiar with their institution's chest pain protocol. High priority should be given to patients with chest pain. Ideally, the emergency department will be notified that a patient with chest pain is arriving, as such patients should be transported by EMS.

The two primary goals of the initial evaluation in the emergency department are to determine the likelihood that an individual has ACS and to estimate the short-term risk of adverse outcome(s) [3]. The findings of the history, physical examination, ECG, and cardiac troponin levels have been integrated into risk assessment scores and clinical prediction algorithms to help identify patients at increased risk of adverse outcomes. Identifying patients at high risk is most important, as these patients will gain the greatest absolute benefit from appropriate therapy [2; 3]. Because timely, appropriate treatment depends on results of the clinical findings and diagnostic testing, it is essential that this information is obtained as quickly as possible.

Although a large percentage of individuals with suspected ACS will be seen initially in emergency departments, patients in any healthcare setting, regardless of other diagnoses, may abruptly develop chest pain suspicious for ACS.

Consider these simulated clinical situations:

Patient I walked into the triage area of the local emergency department. He stated that his primary care physician instructed him to come to the emergency department because his angina attacks were "getting worse." He stated that his physician instructed him to come in an ambulance, but he drove himself. The triage nurse noted that the patient was diaphoretic and in distress. When asked, the patient admitted that he was currently experiencing "some discomfort" in his chest that started when he walked into the hospital from the remote parking area. An ECG showed characteristic ST-segment elevation indicative of an anterior wall MI.

Patient Q was admitted to outpatient surgery for an elective procedure. Her preoperative work-up the day prior to admission showed normal laboratory values and ECG. Her admitting vital signs on the day of surgery were within normal limits. While Patient Q was in the preoperative holding area, she told the nurse that she was experiencing "some weirdness" in her chest. With questioning, she described the sensation as burning and the location as "my chest; no, I can't point to one place, but it hurts a lot." The nurse noted that Patient Q looked anxious and in distress; her respiratory rate increased to 24 breaths per minute, her blood pressure rose to 180/94 mm Hg, and her telemetry monitor showed that she was having isolated premature ventricular contractions (PVCs). Patient Q's initial ECG was negative for indications of ischemia, but her initial set of cardiac biomarkers came back positive for myocardial damage.

Patient J, a man 82 years of age, was admitted to an inpatient medical-surgical unit with a diagnosis of community-acquired pneumonia. He was treated with antibiotics and nebulizer treatments, but he developed a productive cough and complained intermittently about pain in his ribs from coughing. Three or four days after admission, Patient J told the nurse, "I think my pneumonia is getting worse. I have this terrible pain in my chest, and I'm not coughing anything up." When asked,

RISK FACTORS FOR CHD ACCORDING TO RACE/ETHNICITY AMONG PATIENTS WITH ACS					
Patient Characteristics	**White**	**Black**	**Hispanic**	**Native American**	**Asian**
Age	63.9 years ±13	59.4 years ±13	61.3 years ±13	58.7 years ±12	63.7 years ±12
Male gender	62%	50%	61%	62%	61%
Risk Factors					
Family history of CHD	42%	38%	37%	42%	28%
Hypertension	69%	81%	71%	70%	75%
Diabetes	28%	40%	44%	54%	37%
Current smoker	26%	31%	22%	38%	16%
ACS = acute coronary syndrome; CHD = coronary heart disease.					
Source: [109]					*Table 6*

Patient J described the pain as severe discomfort located on the left side of his chest. A check of vital signs showed that Patient J's heart rate was 110 beats per minute and his oxygen saturation on room air was 88%. He was diaphoretic but denied nausea. "I'm just tired, really tired," he reported. "I haven't felt this bad before. I thought I was getting better." An initial 12-lead ECG showed changes suspicious for myocardial ischemia.

When a patient complains of symptoms suspicious for ACS, ACCF/AHA guidelines recommend [2; 3]:

- Early risk stratification (for risk of death or re-infarct) should be done for any person who presents with chest discomfort or other ischemic symptoms.
- Risk stratification includes patient history, assessment of chest pain, physical findings, ECG findings, and cardiac biomarkers.

DIAGNOSIS

PATIENT HISTORY AND PHYSICAL EXAMINATION

What traditional cardiac risk factors are more common in women than men?

The integration of the clinical presentation and history with ECG findings, cardiac biomarker levels, and results of cardiac imaging is essential for determining an accurate diagnosis, assessing risk, and guiding subsequent therapy. A carefully taken patient history is essential to elicit the details needed to make an accurate diagnosis. The medical history should focus not only on the type of pain the individual is having but also on risk factors that may predispose the patient to ACS. Information to obtain includes [2; 3; 34; 100]:

- Time symptoms began
- Identification of contraindications to potential treatment measures
- Medications the patient is currently taking
- Allergies
- Risk factors for CHD
- History of previous admissions for chest pain or ACS
- Past history of intervention for CHD/ACS, including PCI and coronary artery bypass graft (CABG) surgery
- Known cerebral vascular or peripheral vascular disease

Research has shown that a history of traditional cardiac risk factors varies among some subgroups. Women with ACS are more likely than men to have a history of diabetes, hypertension, or hyperlipidemia [11; 101; 102; 103; 104; 105; 106]. (It has been suggested that this is due to the fact that women tend to develop ACS at an older age) [103; 106]. Women are less likely to be smokers, to have a history of angina or MI, and to have had PCI or CABG, regardless of the cardiac history [104; 107; 108]. Data on the prevalence of risk factors across racial/ethnic subgroups with ACS was reported in 2008 (***Table 6***) [109].

The five most important history-related factors that relate to the likelihood of ischemia due to CHD are (in order of importance) [110]:

- Nature of the chest pain
- History of CHD
- Sex/gender
- Age
- Number of traditional risk factors

Among patients who have no pre-existing CHD, older age seems to be the most important factor related to a diagnosis of ACS. An age of older than 55 years for men or older than 65 years for women has been shown to be more important than all other factors [111; 112; 113].

Most often, the physical examination is normal for patients being evaluated for possible ACS. Thus, for these patients the physical examination is important not to establish a diagnosis of ACS but rather to rule out an alternate diagnosis, identify any comorbidities that may have an impact on treatment decisions, and add prognostic information [2; 3]. Ruling out a noncardiac cause of chest pain is especially important given the severity of other possible causes of chest pain [3; 114].

The physical examination should include [3]:

- Evaluation of vital signs
- Determination of the presence of stroke, pulses, and jugular venous distention
- Pulmonary auscultation for rales
- Cardiac auscultation for murmurs and gallops
- Neurologic evaluation
- Evaluation for signs of cardiogenic shock (hypotension and organ hypoperfusion)
- Identification of contraindications to antiplatelet or fibrinolytic therapy

The presence of bruits or pulse deficits (which would suggest extracardiac vascular disease) is associated with a higher likelihood of significant CHD [3]. Similarly, significant CHD is more likely in a patient who has an S3 or S4 gallop, a new mitral insufficiency murmur, or signs of congestive heart failure (pulmonary rales and elevated jugular venous pressures) [115]. Cardiogenic shock is associated more often with STEMI than NSTEMI, and mortality rates are high [3]. Contraindications to antiplatelet or fibrinolytic therapy include any prior intracranial hemorrhage, known malignant intracranial neoplasm, suspected aortic dissection, active bleeding or bleeding diathesis (excluding menses), or significant closed-head or facial trauma within the previous three months [2].

Chest Pain

What is a potentially life-threatening cause of non-ACS chest pain?

Chest pain is the most commonly reported symptom in all patients with ACS, regardless of age, gender, race/ethnicity, or the presence of comorbid conditions [14; 116; 117]. So-called "classic" ACS-related chest pain has been described as diffuse pain or pressure in the substernal or epigastric area that frequently radiates to the neck, jaw, and left arm [22; 101; 118; 119]. Chest pain related to ACS usually begins abruptly and lasts at least 15 to 20 minutes; however, the duration of pain varies among patients [101; 120]. Pain that lasts for longer than 20 minutes is associated with increased short-term risk of MI (nonfatal or fatal) [121]. The intensity of "classic" ACS chest pain increases over time, reaching maximal intensity after a few minutes [101; 122]. Pain is usually worse with activity and improves with rest [101].

DIFFERENTIAL DIAGNOSIS OF CHEST PAIN
Life-Threatening Causes
Aortic dissection
Pulmonary embolism
Pneumothorax
Expanding aortic aneurysm
Other Causes
Pneumonia
Pleuritis
Pericarditis
Costochondritis
Cervical disc disease
Peptic ulcer disease
Gastroesophageal reflux
Biliary disease
Pancreatitis
Panic attack
Source: [3; 114] *Table 7*

The first step in evaluating chest pain is to determine whether the pain is cardiac or noncardiac. Many other conditions can cause chest pain that is similar to cardiac pain, and the physical examination and imaging tests can aid in the differential diagnosis. Chest pain assessment should include time of onset of the pain, description of the pain or discomfort, location of the pain, intensity/severity of the pain, radiation to any other body part, any associated symptoms, how long the pain lasts, and what relieves the pain (***Table 7***) [3; 114].

When medications such as nitroglycerin or morphine are administered, their effectiveness in reducing or relieving chest pain should be noted. In the past, it was thought that cardiac pain could be distinguished from some types of noncardiac pain by assessing the relief of chest pain with use of specific drugs, such as nitroglycerin or antacids. However, relief of chest pain after administration of either of these drugs should not be used to distinguish pain as cardiac or noncardiac in nature. Studies have shown that nitroglycerin may relieve both cardiac and noncardiac chest pain [3]. In one study, nitroglycerin relieved chest pain in 35% of patients with ACS and 41% of patients without ACS [3]. Similarly, a gastrointestinal cause of pain should not be assumed if the chest pain is relieved by antacids, as some patients with ACS have reported relief after use of such a drug [3; 123].

Typical ACS Symptoms

Typical or classic ACS-related chest pain is often described as tightness, sensation of pressure, heaviness, crushing, vise-like, aching, and/or squeezing [101; 124]. Pain features that are not generally characteristic of ACS-related pain include sharp, stabbing pain; pain reproduced with movement or palpation of the chest wall or arms; pain lasting several hours; fleeting pain (episodes lasting for a few seconds or less); burning pain or

heartburn; knot in the chest; lump in the throat; or band-like sensation [3; 101; 115; 122; 123]. The classic presentation of ACS includes some symptoms in addition to chest pain, primarily dyspnea, diaphoresis, nausea, or syncope [14; 22; 125; 126]. Again, there is wide variation in the symptoms reported by patients with ACS, as well as differences in subgroups of patients. Patients with STEMI more commonly report nausea, cold sweats, and vomiting [127]. Several studies have demonstrated an increased prevalence of diaphoresis among men with ACS compared with women [107; 116; 128; 129; 130; 131].

An important distinction between stable angina and UA is that the former is exacerbated by activity or emotional stress and relieved by rest and/or nitroglycerin; in contrast, UA occurs at rest [3]. Pain associated with UA may also be pain previously diagnosed as angina that has increased in frequency, duration, or severity or that is prompted by less exertion than in the past [3].

Atypical ACS Symptoms

An increasing number of studies have demonstrated that atypical chest pain occurs more often in several subgroups of patients, especially women, older individuals, and people with diabetes [14; 102; 117; 126; 131; 132; 133; 134]. In addition, the findings of several studies and literature reviews have demonstrated that women with ACS are more likely to have pain or discomfort in the jaw, neck, throat, arm/shoulder, and back [102; 127; 131]. Failure to recognize atypical symptoms of ACS has been found to delay diagnosis and/or result in the use of less aggressive treatment. It has been estimated that more than 40% of patients with angina have one or more "atypical" elements in their chest pain description [135; 136]. Atypical symptoms that have been found to be associated with ACS include shortness of breath, fatigue, lethargy, indigestion, anxiety, tingling in upper extremities, palpitations, loss of appetite, and flushing. Words commonly used to describe "atypical" chest pain associated with ACS include numbness, tingling, burning, stabbing, or pricking. Atypical chest pain location includes any area other than substernal or left sided, such as the back, area between shoulder blades, upper abdomen, shoulders, elbows, axillae, and ears [135; 136].

Clinical presentation may also differ for older patients. Research has shown that the absence of chest pain is more likely in older patients compared with younger patients. According to study data, 40% of ACS patients 85 years of age or older had chest pain compared with 77% of ACS patients younger than 65 years of age [14]. Older patients with ACS have also been less likely to report arm pain [129].

Few studies have been done to compare reports of chest pain across racial/ethnic groups or according to comorbid conditions. However, studies have demonstrated chest pain of greater intensity and over a greater area in Asian patients (compared with non-Asian patients) and more frequent atypical chest pain (described as stabbing, numbness, or burning) among patients with ACS and diabetes (compared with no diabetes) [110; 111].

Despite this fact, up to one-third of patients with ACS have no chest pain or discomfort [117; 137]. This so-called "silent ischemia" is more likely to occur in persons with diabetes, women, older adults, and persons with heart failure [1; 34]. Thus, the lack of chest pain should not rule out ACS as a diagnosis, especially in the presence of other indicators.

12-LEAD ELECTROCARDIOGRAM (ECG)

Electrocardiography has historically been used to assess myocardial ischemia, and it continues to be an essential diagnostic tool [138]. A 12-lead ECG can be used to [1; 33; 34; 47]:

- Confirm the diagnosis of acute STEMI
- Differentiate between UA/NSTEMI and STEMI
- Identify the affected part of the myocardium
- Diagnose arrhythmias and conduction abnormalities that may occur during ischemia and infarct

Overview of Basic ECG Principles

To understand how 12-lead ECGs can provide information about myocardial ischemia, injury, or infarct, an understanding of the basic electrocardiography principles is necessary. A thorough discussion of 12-lead ECG interpretation in the diagnosis, evaluation, and management of MI exceeds the scope of this course; the information presented below is intended as an introduction and overview only.

The standard 12-lead ECG is a representation of the heart's electrical activity recorded from electrodes on the body surface. In a traditional 12-lead ECG, 10 recording electrodes are placed in designated positions on the patient's arms, left leg, and the left side of the chest. Twelve different recordings of the patient's heart rhythm are taken simultaneously; each records the electrical signals from the heart using a particular combination of the recording electrodes. Each combination of electrodes is referred to as a "lead." Each lead is given a designation that reflects its location and its view of the heart [47].

Some leads look at the bottom (inferior) section of the heart, others monitor what occurs in the anterior wall, and still others monitor the lateral wall. Because of the way the heart is positioned in the thorax, none of the surface leads in a standard ECG directly look at the back of the heart. However, the placement of some leads can be modified to provide more direct information [47].

In normal conduction, the ST segment begins at the end of the QRS complex and stops at the beginning of the T wave. In the cardiac cycle, this segment corresponds to mechanical systole. On ECG, the ST segment normally appears flat and lies along the baseline.

The T wave represents the period of ventricular repolarization. In appearance, the T wave looks asymmetrically rounded. Normally, the T wave is upright in leads I, II, and V [47]. Changes in the ST segment and the T wave can indicate the presence of acute myocardial ischemia and acute MI. The ECG leads in which these changes occur provide information about the part of the heart involved.

General Recommendations for ECG in Patients with Suspected ACS

The ACC/AHA guidelines recommend that a 12-lead ECG be done and interpreted by an experienced physician within 10 minutes after arrival for patients who have chest pain or other signs suggestive of ACS [2; 3]. The diagnostic accuracy of ECG is improved if it is done while the patient is symptomatic, as acute ischemia (and underlying CHD) is strongly suggested by the transient ST-segment changes that occur during symptoms at rest and resolve when symptoms disappear [3]. A 12-lead ECG performed by EMS personnel is recommended for patients who have symptoms consistent with STEMI [2].

A single ECG cannot capture the entire dynamic process of ischemia. As a result, the initial ECG for patients with acute MI can be normal or nondiagnostic in 20% to 55% of cases [82]. Among patients with chest pain and a normal ECG, approximately 1% to 6% will subsequently be found to have MI and about 4% will be found to have UA [3]. Nondiagnostic ECGs are more likely in older patients; according to trial data, the rate of nondiagnostic ECGs was 23% for patients younger than 65 years of age and was 43% for patients 85 years of age and older [14]. In addition, ST-segment elevation on the ECG at presentation has been shown to decrease with age, from 96.3% for patients younger than 65 years of age to 69.9% for patients 85 years of age or older [14]. Thus, the ACC/AHA guidelines state that if the initial ECG is not diagnostic or if the patient remains symptomatic and ACS is suspected, serial ECGs should be done at intervals of 15 to 30 minutes during the first hour [3].

Adherence to the ACC/AHA guidelines for obtaining ECG has been suboptimal, with ECG being performed up to 73% of the time [139; 140]. Delay in obtaining the first ECG has been associated with female gender and older age [14; 141; 142]. This delay may be related to the high rate of atypical presentation of ACS in these populations [14; 143]. Increasing the number of nurses or ECG technicians during peak hours and training additional staff to perform ECGs may help to improve timeliness [144; 145].

ECG Changes Indicative of MI

Three classic ECG characteristics are used in the diagnosis of STEMI: ST-segment elevation, T-wave inversion, and Q-wave formation. During MI, these ECG changes can evolve over minutes to hours. They reflect the impact of the infarction on the functioning of affected myocardial tissue. In STEMI, the damage generally involves the full width of the myocardial wall (from the inner endocardium through the upper epicardium); the term "transmural" is used to designate this type of full-wall thickness damage. The associated ECG changes in STEMI mirror the spread of the damage as it begins in the endocardium and travels outward through the heart wall until the epicardium of the wall is also damaged [1; 34; 47].

The earliest ECG hint of an acute STEMI is an increase in the height of the T wave. Referred to as "hyperacute," these T-wave changes are transient. They are not considered a definitive diagnostic sign but should be taken as highly suspicious for possible acute MI in a patient with clinical symptoms of ACS [1; 34; 47].

The first of the three classic signs is ST-segment elevation. It may be followed by T-wave inversion and pathologic Q-wave formation. This sequence of changes is called the electrocardiographic evolution of an infarction. Because these changes happen over a period of time, a series of 12-lead ECG tracings may be required for accurate diagnosis. In the very early stages of infarct, clear patterns may not be immediately revealed on ECG. As always, ECG findings should be correlated with clinical signs and symptoms. Over a period of months to days, ST-segment elevation and T-wave changes will resolve and no longer be present on 12-lead ECG recordings. Pathologic Q waves, on the other hand, frequently remain permanently. Presence of a pathologic Q wave on 12-lead ECG with no evidence of ST-segment elevation or T-wave changes usually indicates that the person has had an infarct in the past [1; 34; 47]. It is important to note that ST-segment and T-wave changes are not specific for ACS and may be the result of another disease or condition. Left ventricular aneurysm, pericarditis, myocarditis, Prinzmetal angina, Takotsubo cardiomyopathy, early repolarization, and Wolff-Parkinson-White syndrome may cause ST-segment elevation [3]. T-wave inversion can be caused by central nervous system events and treatment with tricyclic antidepressants or phenothiazines.

The ST segment in a normal ECG complex runs along the baseline of ECG. In STEMI, the ST segment lifts upward off the baseline on the ECG tracing, reflecting the movement of injury in the myocardium. ST-segment elevation will be noted in the ECG leads that are facing the affected area of the heart wall. These changes are referred to as changes indicative of infarct. To confirm a diagnosis of STEMI, characteristic ECG changes must be present in two adjacent (contiguous) leads [1; 34; 47; 146].

As an acute MI continues to evolve, the elevated ST-segment will begin to drop. As it drops, the T wave begins to come down to baseline and eventually inverts. When a 12-lead ECG shows evidence of the ST-segment elevation resolving and the T wave inverting, it indicates that the infarction is well along in evolution [47].

ECG CHANGES AND DIAGNOSIS OF STEMI		
Leads Showing Changes	**Location of Infarction**	**Location of Occlusion**
II, III, aVF	Inferior wall	Right coronary artery
I, aVL, V5–6	Lateral wall	Circumflex artery
V1–V4	Anterior wall	Left anterior descending
Reciprocal changes only in V1–V2, sometimes V4	Suspect posterior wall of the heart	Right coronary artery
ST elevation in inferior leads and lead V1	Suspect right ventricular wall	Right coronary artery
Source: [47; 147]		*Table 8*

When an infarct damages the full thickness of the affected wall, the myocardial tissue loses its ability to depolarize and conduct electrical impulses. The tissue becomes electrically inert and generates no electrical activity. When a 12-lead ECG is performed, the area of infarction acts like a "window" that allows ECG monitoring leads to look through the infarct to the opposite wall of the heart. This results in characteristic changes in the recorded ECG pattern. One of these changes is referred to as a pathologic Q wave. Pathologic Q waves are seen in the leads that reflect the infarction. In a normal ECG recording, a Q wave may be present as the first negative deflection of the QRS complex. However, when the Q wave is significantly oversized, it reflects a change in depolarization due to the presence of necrotic tissue. Although a pathologic Q wave can be seen in either STEMI or NTSEMI, it is more common in STEMI. Unlike ST-segment elevation and T-wave inversion, formation of a pathologic Q wave is permanent [34; 47].

It is possible for an acute infarction to occur that causes ST-segment elevation but does not extend damage through the full thickness of the myocardial wall. This type of infarction is sometimes referred to as a subendocardial infarction. It will cause ST-segment changes (elevation initially, then resolving) and T-wave inversion but will not have a Q wave during the acute episode or afterwards. The diagnosis of non-Q wave MI is based on ST-wave changes and T-wave changes. The leads in which the classic signs of STEMI are seen give an indication of what vessel and what wall of the heart are involved (***Table 8***).

Identification of right ventricular acute MI can be difficult because standard ECG lead placement does not provide a good direct view of the right ventricle. If a right ventricular acute MI is suspected, a modified 12-lead ECG may be done in which V leads are placed on the right side of the chest (instead of the left) in corresponding positions. An "R" is added to the lead designation to indicate the change in position [1; 34; 47].

True posterior acute MI may be caused by damage to the posterior wall of the left ventricle. The traditional 12-lead ECG may also be modified to provide additional diagnostic information through use of additional leads (V7–V9) positioned at set points on the patient's back [1; 34; 47].

ECG Changes in NSTEMI

An NSTEMI may be characterized by ST-segment depression and T-wave abnormalities. ST-segment elevation does not occur [47]. Both UA and NSTEMI are characterized by a lack of ST-segment elevation on ECG, so the distinction between the two conditions relies on troponin levels.

During myocardial ischemia, blood flow to the endocardium is reduced first; blood flow to the outer layer of heart (epicardium) remains adequate. As a result, the endocardium experiences significant metabolic changes associated with ischemia while the epicardium does not. These changes alter the electrical potential and current flow through the myocardium. A 12-lead ECG records these changes as ST-segment depression. Measured from the isoelectric line, an ST depression of 1 mm or more below baseline can indicate ischemia. It is important to note, however, that when ST-segment depression is seen in some leads along with ST-segment elevation in other leads, the ST-depression is a reciprocal ECG change associated with STEMI. As always, it is important to place ECG findings within the full context of the patient's symptoms. Because it reflects the changing balance of oxygen supply and demand in the affected coronary artery, ST-segment depression may be present during the period of ischemia only to disappear when the ischemia is relieved. Ischemia can also cause T-wave abnormalities such as T-wave inversion. In NSTEMI, these changes can be difficult to interpret [47].

IMAGING STUDIES

Imaging studies are an important component of evaluation of patients with chest pain.

Chest X-Ray

Chest x-ray is used primarily to rule out other causes of chest pain, such as pulmonary embolus, aortic dissection, and cardiomyopathy [22; 122; 125]. Radiography findings are rarely abnormal in patients with ACS [148].

Echocardiography

In the ACCF/AHA/American Society of Echocardiography guidelines, echocardiography is a class I recommendation for patients with chest pain and suspected ACS when the baseline ECG and biomarkers are nondiagnostic [149; 150]. The guidelines suggest that the test be done while the patient is having pain or within minutes after pain has subsided. The strengths of echocardiography are its ability to assess myocardial thickness, thickening, and motion at rest, and it can aid in risk stratification of patients with suspected UA/NSTEMI [22; 125]. Transient segmental wall motion abnormalities that normalize with treatment support a diagnosis of UA [149; 150]. Persistent wall motion abnormalities indicate more severe, chronic ischemia and a higher risk of adverse events [151]. Echocardiography is also useful for assessing left ventricular function before angiography [151]. The ACCF/AHA guidelines for STEMI note that it is reasonable to use portable echocardiography to clarify a diagnosis of STEMI and to aid in risk stratification [2]. The disadvantages of echocardiography are its inability to distinguish between acute and chronic abnormalities and the need for skilled technicians and interpreters of results [122].

Cardiac Magnetic Resonance Imaging (MRI)

Cardiac MRI has been validated for assessing myocardial function and has a similar capability to echocardiography in the diagnosis of MI [122; 152]. The usefulness of MRI in this setting was studied in 161 consecutive patients who had 30 minutes of chest pain and ECG findings that were nondiagnostic of acute MI. MRI that included perfusion, left ventricular function, and gadolinium-enhanced MI detection was shown to have a sensitivity and specificity of 84% and 85%, respectively, for diagnosing ACS [153]. MRI is not generally used in the acute setting because of the inconvenience of its use [22; 125].

STRESS TESTS

Factors to consider when selecting a stress test are the patient's resting ECG and ability to exercise, as well as local resources. An exercise stress test is the easiest, most cost-effective test and should be the choice unless the patient is unable to exercise or has ST changes on resting ECG (class IC) [3]. ST changes on the resting ECG may interfere with interpretation of the stress test findings, and for patients with ST changes, stress testing with an imaging modality (such as cardiac radionuclide imaging or stress echocardiography) is recommended (class IB). Pharmacologic stress testing with imaging should be done for patients who have limited ability to exercise (class IC). Exercise stress testing should be done and interpreted according to the ACC/AHA guidelines, and the results will dictate the need for further therapy [154].

Exercise Stress Test

Used to evaluate the effects of stress on the heart muscle and coronary blood flow, an exercise stress test involves some type of physical exercise. Walking on a treadmill is a common method. Following a predetermined protocol, the speed of the treadmill and its angle are increased at set intervals. The patient's ECG and blood pressure are monitored. The test is terminated when a target heart rate is achieved or the patient develops symptoms such as chest pain, hypotension, bradycardia, severe hypertension, or ST-segment changes on ECG. Because patients must be physically able to walk on the treadmill, this test is contraindicated for anyone who cannot do so. Chemical stress tests may be used instead. Consumption of caffeine or cigarette smoking is contraindicated for several hours prior to the test. Patients should be instructed to wear comfortable clothes and shoes appropriate for walking on a treadmill; female patients should be directed to wear a bra that provides adequate support. Echocardiogram imaging may be added to an exercise stress test to provide information about the presence or absence of heart wall abnormalities. If echocardiography is included, a baseline test will be performed prior to the exercise part of the test. Immediately following the conclusion of the treadmill portion, the echocardiogram will be repeated [34; 147; 155].

Diagnostic findings from an exercise stress test include [34; 147; 155]:

- Negative: The patient achieves the target heart rate with no symptoms of ischemia. No evidence of new heart wall motion abnormalities are noted on echocardiogram.
- Positive: The patient develops symptoms of ischemia during the test. New heart wall motion abnormalities are evident in the echocardiogram completed after the treadmill portion of the test. Follow-up testing, usually cardiac catheterization, is indicated.
- Equivocal: The patient develops symptoms during the test that are not directly linked to myocardial ischemia, or the patient is unable to achieve the target heart rate but has no symptoms of ischemia. Additional testing is indicated.

Adenosine Thallium Test

Combining a chemical stress test with radionuclide imaging, an adenosine thallium test evaluates the blood supply to the myocardium. This test may be performed in two parts. The patient is kept NPO for 4 to 6 hours prior to the start of the test. Adenosine is injected to increase heart rate, myocardial contractility, and myocardial oxygen demand. Radioactive thallium is injected, and a series of images are taken to assess the adequacy of blood flow to the myocardium. Several hours later, the patient is again scanned to evaluate blood flow to the

myocardium at rest. Adenosine thallium scans may identify site(s) of old infarctions, areas of partial obstruction of blood flow to the myocardium, and areas where blood flow (perfusion) decreases during exercise [34; 147; 155]. In 2013, the FDA issued a warning of a rare but serious risk of myocardial infarction and death associated with adenosine [156]. Adenosine should be avoided in patients with evidence of unstable angina or cardiovascular instability.

Dobutamine Stress Echocardiogram (DSE)

A DSE test may be used to evaluate the heart's response to stress in patients who are unable to physically perform a treadmill exercise test. This test uses IV dobutamine to "stress" the heart by increasing myocardial contractility and heart rate, which in turn increases myocardial oxygen demands. Echocardiogram imaging is done when the patient is at rest and after the dobutamine has been injected to look for wall motion abnormalities [34; 147; 155].

Results may be:

- Negative: The patient's heart rate reaches the target rate, and the patient shows no symptoms of ischemia. Echocardiogram imaging shows no new heart wall motion abnormalities.
- Positive: The patient develops symptoms before reaching the target heart rate and/or new heart wall motion abnormalities are seen on Echocardiogram. Follow-up testing, usually a cardiac catheterization, is indicated.

CARDIAC BIOMARKERS

What is the recommended biomarker for detecting cardiac damage?

Cardiac biomarkers are detectable intracellular macromolecules released into the circulation after cardiomyocyte injury and death. The biomarkers once used—creatinine kinase (CK)-MB and myoglobin—have been replaced by cardiac-specific troponin (troponin I or T) because of the latter's high concentration in myocardium, near-absolute specificity for myocardial tissue, their absence in the blood of healthy individuals, and their high clinical sensitivity [2; 3; 22]. Measurement of CK-MB or myoglobin levels was not useful or cost-effective [157].

Cardiac Troponins

As noted, cardiac troponin I and T are sensitive and specific biomarkers of myocardial injury, and serum measurements are used to identify whether patients with ACS have had an MI. A variety of troponin assays are in use. Contemporary ("sensitive") troponin assays have been in use for many years, while "highly sensitive" assays were only approved in 2017 for use in the United States. The Fourth Universal Definition of MI recommends using highly sensitive troponin assays when available [22].

The time to initial elevation of cardiac troponin levels following MI is 2 to 12 hours when measured by sensitive assays, with peak elevation at 24 hours (troponin I) and 12 to 48 hours (troponin T) [3; 158]. Levels may remain elevated for 5 to 10 days (troponin I) or up to 14 days (troponin T) after an MI [158]. Highly sensitive assays detect significant elevations of cardiac troponin within one hour, which has the advantage of more rapid diagnosis and triage. The sensitivity of cardiac troponin for the diagnosis of MI is relatively low during the first six hours, especially in patients who present shortly after symptom onset [158]. However, for most patients with ACS, MI can be ruled out or confirmed within six hours, in part because of the high rate of delayed presentation associated with chest pain [3].

For the diagnosis of MI, the fourth universal definition of MI defines myocardial injury as a rise and/or fall in cardiac troponin of at least one value above the 99th percentile of the URL for normal values, including evidence of serial increases or decreases of troponin levels [22]. Similarly, the recommendations based on the findings of a Laboratory Medicine Best Practices systematic review are the use of cardiac troponin assays only (no additional biomarkers), with the 99th percentile URL used as the clinical diagnostic threshold for a diagnosis of NSTEMI [159].

It is important to bear in mind that chronic elevations of troponin are present in some patients unrelated to acute events, which is why a rise or fall of troponin is required to establish the diagnosis of MI. Baseline troponin levels are often higher in the elderly than in younger adults; 20% of adults older than 70 years of age have, as baseline, a cardiac troponin level above the 99th percentile URL [160]. Troponin assays are not standardized; the value reported will vary depending on the assay used, and comparison of reported results across different laboratories may not be reliable for diagnostic purposes [22]. Clinicians should familiarize themselves with the specific assay used in their own facility.

The ACC/AHA guideline for UA/NSTEMI states that troponin levels should be measured at the time of presentation and three to six hours after the onset of symptoms in all patients suspected of having ACS [3]. If the time of symptom onset is unclear, the time of presentation should be used instead. When initial serial troponin levels are normal but ECG changes and/or clinical features increase the suspicion for ACS, additional troponin levels should be measured beyond six hours [3]. The lack of elevated troponin levels at the time of presentation should not rule out an MI, as the initial level is normal in as many as 23% of patients with MI [161]. The lack of elevated troponin levels at the time of presentation should not rule out an MI, as the initial level is normal in as many as 23% of patients with MI [161]. Troponin levels appear to have value in ruling out an MI; the negative predictive value of undetectable troponin levels has been reported to be 99% to 100%.

A diagnosis of MI should not be made on the basis of a single elevated troponin level, as elevated levels may be associated with other cardiac conditions, including tachyarrhythmia, high or low blood pressure, cardiac trauma, heart failure, myocarditis, and pericarditis [3].

Other Markers

As noted earlier, CK-MB, myoglobin, and other biomarkers are no longer useful in diagnosing ACS. B-type natriuretic peptide (BNP) and N-terminal proBNP are also not useful as an aid to diagnosing ACS, but they have demonstrated strong predictive value for short- and long-term mortality for patients with ACS, and the ACC/AHA guideline notes that these biomarkers may be considered to assess risk in patients in whom ACS is suspected (class IIbB) [3; 162; 163].

COMPREHENSIVE RISK SCORE AND PROGNOSIS

Risk stratification is an integral component of diagnosis, especially for patients with UA/NSTEMI. The risk of cardiac death and ischemic events varies widely in the UA/NSTEMI population, and the prognosis can help inform decision making regarding treatment [2]. The ACC/AHA guidelines for UA/NSTEMI and STEMI recommend risk assessment with either the Thrombolysis in Myocardial Infarction (TIMI) risk score or the GRACE risk model [2; 3]. The TIMI risk score predicts 30-day and one-year mortality and was developed in a population of patients with STEMI; the GRACE model predicts in-hospital and six-month mortality for all patients with ACS [2; 3].

The TIMI risk score is based on seven independent risk factors [164]:

- Advanced age (65 years or older)
- At least three risk factors for CHD
- Previous coronary artery stenosis of 50% or more
- ST-segment deviation on initial ECG
- At least two episodes of angina in the past 24 hours
- Use of aspirin in the past 7 days
- Elevated levels of cardiac biomarkers

One point is given for each factor, and the total score corresponds to the risk of all-cause mortality, new or recurrent MI, or severe recurrent ischemia requiring urgent revascularization through 14 days [164]. That risk ranges from 4.7% for a TIMI risk score of 0 or 1 to 40.9% for a score of 6 or 7. Patients with a higher TIMI score will derive greater benefit from an invasive strategy [3]. The TIMI risk calculator can be accessed online at http://www.timi.org.

The GRACE risk model includes eight variables [165]:

- Age
- Killip class
- Systolic blood pressure
- ST-segment deviation
- Cardiac arrest during presentation
- Serum creatinine level
- Elevated cardiac biomarkers
- Heart rate

Points are assigned to each factor, and the sum total corresponds to a probability of in-hospital death, ranging from 0.2% or less for up to 60 points to more than 52% for a sum of 250 points or more [165]. As with the TIMI score, patients with a higher score gain greater benefit from an invasive strategy [3]. The GRACE risk tool is also available online (https://www.outcomes-umassmed.org/grace).

Clinical features, ECG findings, and troponin levels also may be used to determine both early- and long-term prognosis and direct treatment. For example, patients with elevated troponin levels will benefit from intensive management and early revascularization [3]. In addition, elevated troponin levels have been associated with an estimation of infarct size and the risk of death [3]. With regard to ECG findings, after confounding ECG patterns (i.e., bundle-branch block, paced rhythm, left ventricular hypertrophy), the highest risk for death has been associated with ST-segment deviation (elevation or depression) [3]. Isolated T-wave inversion or normal ECG findings were associated with intermediate and low risk, respectively [3]. In another study, the incidence of death or MI at 1 year was significantly higher for patients who had ST-segment deviation of at least 1 mm and an elevated troponin level (18%) compared with patients who had deviation of less than 1 mm (11%) [166].

FINAL DIAGNOSIS

Four diagnoses are possible after complete evaluation for possible ACS: a noncardiac diagnosis, chronic stable angina, possible ACS, and definite ACS.

Risk assessment factors are used to help identify people who are at low risk of ACS and can thus be discharged safely. In one study, short-term clinically relevant adverse cardiac events were rare among patients who had "nonconcerning" vital signs, nonischemic findings on ECG, and no elevated troponin levels on serial testing [167]. Accelerated diagnostic protocols have been developed to help identify patients who can be safely discharged. According to one such protocol, a TIMI score of 0, no new ECG changes, and nonelevated troponin levels at 0 and 2 hours after the time of presentation indicates a low risk of ACS, with no major adverse cardiac events occurring within 30 days after discharge [168; 169]. Another risk stratification tool, the HEART score (consisting of history, ECG findings, age, risk factors, and troponin levels) has been validated in the Netherlands [170]. The HEART score has been shown to identify patients at low risk for ACS and major adverse cardiac events [170]. When compared with care according to ACC/AHA guidelines, a protocol consisting of the HEART score and troponin levels at 0 and 3 hours, led to an increased number

of early discharges, with no major adverse cardiac events at 30 days; shorter lengths of stay, and a decrease in objective cardiac testing over 30 days [171].

The ACC/AHA guideline for UA/NSTEMI includes no class I recommendations for discharge from the emergency department. For patients with possible ACS but normal ECG and troponin levels, the guideline notes that it is reasonable to [3]:

- Observe in a chest pain unit or telemetry unit and perform serial ECGs and cardiac troponin levels at intervals of three and six hours (class IIaB)
- Order a treadmill ECG (class IIaA), stress myocardial perfusion imaging, or stress echocardiography (class IIaB) before discharge or within 72 hours after discharge
- Perform coronary CT angiography to assess coronary artery anatomy (class IIaA) or rest myocardial perfusion imaging with a technetium-99m radiopharmaceutical to exclude myocardial ischemia (class IIaB)

Patients with chronic stable angina should be treated according to the ACC/AHA guidelines [172]. Patients who are discharged from the emergency department should be told to see their primary care physician as soon as possible, preferably within 72 hours [3]. The results of all diagnostic testing in the emergency department should be sent to the primary care physician to ensure continuity of care. Patients with definite ACS should be treated according to the type of MI.

TREATMENT OF UA/NSTEMI

According to data from several studies and quality improvement initiatives, adherence to ACC/AHA guidelines has improved since the early 2000s, but is still not optimal. In addition, time is needed for clinicians to become familiar with updates to clinical practice guidelines; the ACC/AHA guideline for UA/NSTEMI was revised in 2014.

The ACC/AHA guideline reflects the research advances made in ACS. Many more treatment options are available, and clinicians should be familiar with the choices in order to select a strategy on the basis of an individual's status and preference. The most substantial changes in the updated 2014 guideline relate to the following issues [3]:

- More potent antiplatelet and anticoagulant therapy
- Benefit of guideline-directed medical therapy for low-risk patients
- Proper selection of older individuals and women for interventional therapy
- Expanded recommendations on discharge, including patient education, dual antiplatelet therapy, and referral to cardiac rehabilitation

GENERAL CARE MEASURES

The general care of patients with UA/NSTEMI is directed at the severity of symptoms. Bed rest is recommended while patients have ischemic pain. After symptoms have subsided, patients may move to a chair. The ACC/AHA guideline notes that there is no benefit to the routine use of supplemental oxygen, and it may, in fact, even be harmful [3]. Instead, supplemental oxygen should be given only to patients who have an arterial oxygen saturation of less than 90%, respiratory distress, or other high-risk features of hypoxemia. Continuous ECG monitoring should also be carried out, not only to detect ECG changes that may provide additional diagnostic and prognostic information but also because sudden ventricular fibrillation is the primary preventable cause of death during this initial period [3].

ANALGESIC AND ANTI-ISCHEMIC THERAPY

What is the initial drug of choice for relief of acute chest pain in all patients with suspected ACS?

The goal of immediate treatment for patients with UA/NSTEMI is to provide relief of ischemia and to prevent recurrent adverse ischemic events [3]. This is initially achieved through anti-ischemic, antiplatelet, and anticoagulant therapies (***Table 9***).

Analgesic and anti-ischemic therapy for UA/NSTEMI involves the use of nitroglycerin, morphine, beta blockers, calcium-channel blockers, and angiotensin-converting enzyme (ACE) inhibitors. These agents will help alleviate pain through their mechanisms of action. No NSAIDs should be given because of the documented increased risk of major adverse cardiovascular events [3].

Nitroglycerin

Nitroglycerin is a vasodilator that relieves ischemia-related pain by reducing myocardial oxygen demand and enhancing oxygen delivery. Nitroglycerin can be given as sublingual tablets every five minutes for up to three doses. Nitroglycerin (and all nitrates) is contraindicated when a phosphodiesterase inhibitor has been used recently [3]. Nitrates are used with caution in patients with right ventricular infarction.

Patient A was admitted from the emergency department to an inpatient telemetry/stepdown unit with a diagnosis of ACS. Both the patient's initial cardiac biomarkers and initial ECGs were negative for indications of MI. However, because his initial symptoms (increased severity of chest pain, chest pain at rest) coupled with his history of PCI six months ago for an occlusion in his right coronary artery are highly suspicious for ACS, the physician admitted him for on-going observation and monitoring. A few hours after admission to the inpatient unit, Patient A experienced a chest pain attack at rest. He described the pain simply as "bad," 10/10 on the pain scale, and located in the left substernal area of his chest. His admitting medical orders included nitroglycerin, one tab sublingually every five minutes for chest pain, which may be repeated every five minutes to a maximum of three doses as needed. The nurse obtained an ECG and notified the physician.

ADJUNCTIVE TREATMENT INDICATIONS FOR PATIENTS WITH UA/NSTEMI OR STEMI			
Adjunctive Therapy	**UA/NSTEMI**	**STEMI**	**Comments**
Analgesia			
Nitroglycerin	All patients, unless contraindicated (class IC)	No recommendation	Contraindicated for patients with hypotension or who have used sildenafil or vardenafil within previous 24 hrs or tadalafil within previous 48 hrs (class IIIB).
	All patients, unless contraindicated (class IB)	No recommendation	
Morphine	Reasonable for patients who have chest pain unrelieved by maximally tolerated anti-ischemic medications (class IIbB)	Not specifically recommended. Narcotics should be considered if high-dose aspirin fails to relieve pain (class IIbC)	—
Anti-Ischemia Therapy			
Beta blocker	All patients, unless contraindicated (class IA) Continue during and after hospitalization, unless contraindicated (class IC) Re-evaluate patients with initial contraindications to beta blockers for subsequent use (class IC)	All patients, unless contraindicated (class IB) Continue during and after hospitalization, unless contraindicated (class IB) Re-evaluate patients with initial contraindications to beta blockers for subsequent use (class IC)	Administer in the first 24 hours. Contraindicated for patients with signs of heart failure, evidence of low-output state, increased risk of cardiogenic shock, or other contraindications to beta blockers.
ACE inhibitor	Started and continued in all patients with left ventricular ejection fraction less than 40% and in patients with hypertension, diabetes, or stable CKD, unless contraindicated (class IA)	All patients (within the first 24 hours) with anterior location, HF, or ejection fraction less than or equal to 0.40, unless contraindicated (class IA)	Contraindicated for patients with hypotension (systolic blood pressure of <100 mm Hg or <30 mm Hg below baseline). An angiotensin receptor blocker should be used for patients intolerant of ACE inhibitors.
Calcium-channel blocker	Patients with continued or recurrent ischemia or with contraindications to beta blockers (class IB)	No recommendation	—
Antiplatelet Therapy			
Aspirin (non-enteric coated, chewable)	All patients (class IA) Continued indefinitely	All patients (class IA) Continued indefinitely	Should be given as soon as possible at time of evaluation. Contraindicated for patients who have aspirin allergy or active bleeding. Lower dose is reasonable during initial period post-stent implantation in patients at risk of bleeding. Consider clopidogrel or warfarin if aspirin is contraindicated. Monitor closely.
Clopidogrel	All patients (class IB) Administer to patients who are unable to take aspirin (class IB) Maintenance dose daily, continued preferably for up to 1 year (class IB)	All patients (in addition to aspirin), before or at the time of PCI, if not already started and who are undergoing PCI within 24 hours of receiving fibrinolytic therapy (class IC) Daily dose should be continued for 1 year (class IC)	Loading dose not recommended for older (>75 years of age) patients with STEMI. Should be withheld for 5 days in patients to have CABG (class IB). Monitor closely when used in conjunction with warfarin.

Table 9 continues on next page.

ADJUNCTIVE TREATMENT INDICATIONS FOR PATIENTS WITH UA/NSTEMI OR STEMI *(Continued)*			
Adjunctive Therapy	**UA/NSTEMI**	**STEMI**	**Comments**
Antiplatelet Therapy *(Continued)*			
Prasugrel	Not recommended for initial platelet therapy. All patients undergoing PCI with stenting should be given a loading dose and at least 1 year of maintenance therapy with this or other P2Y inhibitor if not given clopidogrel (class IB).	All patients undergoing PCI with stenting should be given a loading dose and at least 1 year of maintenance therapy with this or other P2Y inhibitor if not given clopidogrel (class IB). Should not be given sooner than 24 hours after administration of a fibrin-specific agent or 48 hours after administration of a non-fibrin-specific agent (class IIaB)	Should be withheld for at least 7 days in patients to have CABG (class IB). Should not be administered to patients with history stroke or transient ischemic attack (class IIIB).
Ticagrelor	All patients undergoing PCI with stenting should be given a loading dose and at least 1 year of maintenance therapy with this or other P2Y inhibitor if not given clopidogrel (class IB).	All patients (in addition to aspirin) undergoing PCI with stenting should be given a loading dose and at least 1 year of maintenance therapy with this or other P2Y inhibitor if not given clopidogrel (class IB).	Should be withheld for at least 5 days in patients to have CABG (class IB). May only be used with lower doses (81 mg) of aspirin. Requires twice daily administration.
Glycoprotein IIb/IIIa inhibitor	Patients selected for early invasive treatment, along with dual-antiplatelet therapy, who are at intermediate or high risk (high troponin levels) (class IIbB)	Reasonable for selected patients who are receiving unfractionated heparin to have abciximab with primary PCI (class IIaA); eptifibatide or tirofiban may also be considered with primary PCI (class IIaB) May be reasonable to administer in emergency department to patients selected for primary PCI (class IIbB)	The rate of IV infusion of eptifibatide or tirofiban should be reduced by 50% for patients with estimated creatinine clearance <50 mgL/min. Eptifibatide or tirofiban should be discontinued 2 to 4 hours before CABG (class IB).
Anticoagulant Therapy			
Unfractionated heparin (UFH)	Option for patients selected for early invasive treatment (class IB) and early conservative treatment (class IB) Dose adjusted according to hospital protocol to maintain therapeutic anticoagulation for 48 hrs or until PCI (class IB)	Option for patients selected for primary PCI (class IC) or fibrinolytic therapy (class IC); administer for at least 48 hrs or until revascularization	The UFH dose should be reduced when a glycoprotein IIb/IIIa inhibitor is also given (class IC). For patients undergoing PCI after receiving anticoagulant regimen, administer additional boluses of UFH as needed to support procedure (class IC).
Enoxaparin	Option for patients selected for early invasive treatment (class IA) and early conservative treatment (class IA)	Option for patients selected for fibrinolytic therapy (class IA); administer for at least 48 hours; for use up to 8 days or until revascularization	Discontinue enoxaparin 12 to 24 hrs before CABG (class IB). Reduce dose for creatinine clearance less than 30 mL/min and/or ≥75 yrs of age.

Table 9 continues on next page.

ADJUNCTIVE TREATMENT INDICATIONS FOR PATIENTS WITH UA/NSTEMI OR STEMI *(Continued)*			
Adjunctive Therapy	**UA/NSTEMI**	**STEMI**	**Comments**
Anticoagulant Therapy *(Continued)*			
Bivalirudin	Option for patients selected for early invasive treatment (class IB)	Preferred over UFH with glycoprotein IIb/IIIa inhibitor in patients selected for PCI at high risk of bleeding (class IIaB) Useful supportive measure for primary PCI with/without prior treatment with UFH (class IB)	Reduce dose for creatinine clearance less than 30 mL/min. Discontinue bivalirudin 3 hrs before CABG (class IB).
Fondaparinux	Option for patients selected for early invasive treatment (class IB) and early conservative treatment (IB)	Option for patients selected for fibrinolytic therapy (class IB)	Should not be used as sole anticoagulant to support PCI in patients with NSTE-ACS due to an increased risk of catheter thrombosis. Avoid for creatinine clearance less than 30 mL/min. Discontinue 24 hrs before CABG.
ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft; CKD = chronic kidney disease; HF = heart failure; PCI = percutaneous coronary intervention.			
Source: [2; 3]			*Table 9*

SIZE OF TREATMENT EFFECT FOR RECOMMENDED INTERVENTIONS	
Class	**Predicted Treatment Effect**
I	Benefit >>> Risk Procedure/treatment should be performed/administered.
IIa	Benefit >> Risk (Additional studies with focused objectives needed) It is reasonable to perform procedure/administer treatment.
IIb	Benefit ≥ Risk (Additional studies with broad objectives needed; additional registry data would be helpful) Procedure/treatment may be considered.
III	No Benefit (Procedure/test not helpful; no proven benefit) OR Harm (Procedure/test excess cost without benefit or harmful; treatment harmful to patients)

LEVEL OF EVIDENCE	
Level	**Supporting Evidence**
A	Multiple randomized clinical trials or meta-analyses
B	Single randomized trial or nonrandomized studies
C	Consensus opinion of experts, case studies, or standard-of-care

In this case example, the patient's chest pain is characteristic of ischemic chest pain: its intensity is "severe," it is located in the left substernal area of his chest, and it occurred at rest. The immediate response should be to check Patient A's vital signs and to administer sublingual nitroglycerin as ordered.

Administering Nitroglycerin

Prior to administering sublingual nitroglycerin, the patient's blood pressure should be checked. If the patient is hypotensive, sublingual nitroglycerin should not be administered and the physician should be notified. Intravenous morphine may be ordered for pain relief instead. If the patient's blood pressure is normal or elevated, sublingual nitroglycerin may be administered as follows [1; 34; 173]:

- Obtain an initial pain rating for the patient's chest pain.
- Administer one sublingual nitroglycerin tablet. The tablet should produce a mild burning sensation under the tongue.
- Wait five minutes, then recheck the patient's vital signs and chest pain intensity.

- Carefully document the episode, including pain ratings, vital signs, and medications administered, in the appropriate part of the patient's medical record.

After a single nitroglycerin tablet, Patient A reported that his chest pain dropped to 4 on a scale of 10, and his blood pressure remained slightly elevated.

Ongoing chest pain indicates continuing ischemia. If the patient's blood pressure has not dropped significantly, a second nitroglycerin tablet should be given. If the patient becomes hypotensive from the first dose, no additional doses should be given and the physician should be notified. Morphine, if ordered, may be given as another drug of choice to relieve chest pain. If the patient's chest pain drops to 0 after the second nitroglycerin tablet, no additional tablets are indicated. However, if the patient's pain persists (even at a low level) and blood pressure remains stable, a third tablet should be given.

Per physician orders, an ECG should be obtained if Patient A has chest pain. Ideally, the ECG would be taken while the patient is still having chest pain. Clinically significant signs of myocardial ischemia, such as ST depression and T-wave inversion, may be seen on 12-lead ECG during chest pain episodes.

A major side effect of nitroglycerin is severe headache. Orders for acetaminophen may be effective in reducing the patient's headache. However, some patients will decline further nitroglycerin therapy due to the discomfort of the associated headache. The patient's physician should be notified if the patient is having chest pain and refusing nitroglycerin.

After administration of two sublingual nitroglycerin tablets, Patient A's chest pain was relieved. He reported that he was chest pain free. One hour later, he again developed chest pain and required a third sublingual nitroglycerin tablet for relief. His blood pressure was elevated during this attack; when his pain was relieved, his blood pressure returned to his baseline normal. Less than one hour later, Patient A developed a third bout of chest pain. He rated the pain as 10/10, and his blood pressure increased to 190/120 mm Hg. Three sublingual nitroglycerin tablets again reduced his chest pain to 0 and his blood pressure decreased to baseline. Because the chest pain episodes are increasing in frequency and intensity, the physician decided to initiate a continuous nitroglycerin drip.

The ACCF/AHA guidelines note that if pain is not relieved, continuous intravenous nitroglycerin may be started; the indications for intravenous nitroglycerin are persistent ischemia, hypertension, or heart failure, following administration of sublingual nitroglycerin and a beta blocker [3]. If ischemia recurs, the rate of infusion may be increased until symptoms are relieved. The administration of intravenous nitroglycerin should be discontinued within 24 hours after the patient's condition has stabilized, at which point oral nitroglycerin can be given. Discontinuation of intravenous nitroglycerin should be gradual, as the abrupt cessation has been associated with exacerbation of ischemic changes on ECG [3].

Depending on the hospital's policy and procedure, nitroglycerin may be ordered in micrograms per minute or as a weight-based calculation (i.e., micrograms per kg per minute). The physician's order should specify the starting dose and rate, the maximum dose and rate, and whether or not the infusion can be increased until the patient is free of chest pain, the maximum dose has been achieved, or the patient becomes hypotensive. Nursing responsibilities include [1; 34; 173]:

- Monitoring the patient's blood pressure frequently while increasing/titrating the infusion
- Maintaining the patient on continuous ECG monitoring
- Monitoring the effect of the nitroglycerin on the patient's chest pain
- Notifying the physician if the patient becomes hypotensive
- Notifying the physician if the maximum specified dose is reached and the patient continues to have chest pain

Morphine

The 2014 ACCF/AHA guideline states that morphine is an option for patients who do not have relief of ischemia-related symptoms during treatment with intravenous nitroglycerin or for patients who have recurrence of symptoms during anti-ischemic therapy [3]. If morphine is used in conjunction with intravenous nitroglycerin, the patient's blood pressure should be closely monitored, as hypotension is a potential adverse effect.

Beta Blockers

The inhibition of beta-1 adrenergic receptors by beta blockers acts to decrease cardiac work and myocardial oxygen demand. Beta blockers also slow the heart rate, which helps enhance coronary blood flow. A beta blocker should be given orally to all ACS patients (unless contraindicated) within 24 hours of presentation [3]. This use of beta blocker therapy has been associated with significantly lower in-hospital mortality [174]. Contraindications include signs of heart failure, low-output state, increased risk of cardiogenic shock, or other relative contraindications to beta blockade.

Patient A continued to experience severe chest pain; initiation and titration of the nitroglycerin infusion to higher doses did not relieve his pain. ECG showed ST depression in the inferior leads, and his most recent cardiac biomarkers indicated that his troponin levels were positive for myocardial damage. The physician was notified and ordered morphine 2 mg. Patient A remained hypertensive, and his chest pain persisted at a lower intensity (5/10). The physician ordered 5 mg IV of metoprolol to be administered immediately and 25 mg metoprolol to be taken by mouth twice a day.

Nursing responsibilities in the administration of IV metoprolol include maintaining the patient on continuous ECG monitoring; monitoring blood pressure before, during, and after administration; and monitoring heart rate and rhythm before, during, and after administration. Contraindications to metoprolol (or other beta blocker) administration include bradycardia and hypotension [173].

Calcium-Channel Blockers

Calcium-channel blockers act to inhibit contraction of myocardial and smooth muscle and cause vasodilation, although the agents in this drug class vary in the degree of vasodilation and myocardial contractility they produce [3]. They also relieve (or prevent) signs and symptoms of ischemia by decreasing heart rate and blood pressure.

The strongest evidence for a benefit of calcium-channel blockers in the setting of UA/NSTEMI primarily relates to symptom control. Calcium-channel blockers are indicated for patients who have UA/NSTEMI and [3]:

- Ongoing or recurring ischemia-related symptoms despite adequate doses of nitroglycerin and beta blockers
- Intolerance of adequate doses of nitroglycerin or beta blockers

The four agents used most commonly are nifedipine, amlodipine, verapamil, and diltiazem. Although data on comparisons of these four drugs are limited, verapamil and diltiazem are recommended because of their negative inotropic actions and negative chronotropic and dromotropic effects [3]. The ACC/AHA guideline recommends that a nondihydropyridine calcium channel blocker (verapamil or diltiazem) be given to patients with UA/NSTEMI who have continuing or frequently recurring ischemia and a contraindication to beta blockers, provided that clinically significant left ventricular dysfunction, increased risk for cardiogenic shock, a PR interval greater than 0.24 second, or second- or third-degree atrioventricular block without a cardiac pacemaker are not present [3]. In addition, oral nondihydropyridine calcium antagonists are recommended (unless contraindicated) for patients who have recurrent ischemia after appropriate use of beta blockers and nitrates. Immediate-release nifedipine is not recommended for routine use because of a dose-related increase in mortality [3].

Nursing responsibilities when administering calcium-channel blockers include monitoring heart rate and blood pressure prior to administering the medication. In some patients, calcium-channel blockers may cause hypotension and bradycardia. Special caution should be taken if the patient is taking other medications, such as ACE inhibitors, that can lower blood pressure. Especially in the elderly, use of multiple medications will have an additive effect and will be more likely to cause hypotension, orthostatic hypotension, and an increased risk of falls [173].

Angiotensin-Converting Enzyme Inhibitors

An ACE inhibitor should be administered orally within the first 24 hours (unless contraindicated) to patients who have pulmonary congestion or a left ventricular ejection fraction (LVEF) less than 40%, and to patients who have hypertension, diabetes mellitus, or stable chronic kidney disease [3]. The guidelines also note that an angiotensin-receptor blocker (ARB) should be given to patients who cannot tolerate an ACE inhibitor and have signs of heart failure or LVEF of less than 40%. The benefits of ACE inhibitors have been demonstrated primarily in the long-term setting after MI, with significant reductions in adverse outcomes, including survival at 30 days [3; 175; 176].

When administering ACE inhibitors, the following nursing actions should be taken [173]:

- Monitor blood pressure for hypotension. Be alert for orthostatic hypotension and syncope.
- Implement fall precautions as indicated by patient status.
- Monitor serum potassium levels and renal function studies; elevated serum potassium levels or increasing signs of renal insufficiency/failure can be an indication that the medication should be discontinued.
- Monitor for the development of intolerable side effects. A common and often fatiguing side effect is a dry, nagging cough.

ARBs such as valsartan and candesartan may be prescribed for persons who cannot tolerate ACE inhibitors [177]. When administering ARBs, the nurse should monitor serum electrolytes, renal function studies, and vital signs, especially blood pressure [173]. Hypotension and orthostatic hypotension may result.

Cholesterol Management

Among patients with UA/NSTEMI, treatment with statins has been shown to be associated with lower rates of recurrent MI, CHD-related mortality, need for myocardial revascularization, and stroke [3]. These benefits have been greater with a high-intensity statin (such as atorvastatin) than with low- or moderate-intensity statins. Thus, the 2014 ACC/AHA guideline recommends that all patients receive high-intensity statin therapy, unless contraindicated [3].

ANTIPLATELET THERAPY

Aspirin continues to be a key element in the treatment of patients with UA/NSTEMI as part of overall antiplatelet therapy and reduces rates of recurrent MI and death [3]. Antiplatelet therapy reduces platelet formation and aggregation, integral components in the formation of a thrombus after plaque disruption.

Aspirin

The ACC/AHA guideline recommends that aspirin be given as soon as possible after a patient arrives in the emergency department and continued indefinitely in patients who tolerate it [3]. However, adherence by emergency medical personnel to guidelines recommending prompt prehospital aspirin administration is only 45% [178]. Aspirin is contraindicated for patients who are allergic to the drug or who have active bleeding; clopidogrel is recommended for patients who cannot tolerate aspirin [3]. Aspirin should be nonenteric-coated and chewable, and the recommended dose is 162–325 mg. A maintenance dose of aspirin should be continued indefinitely, at a daily dose of 81–325 mg. Adherence to the recommended use of aspirin has been better than for other drug therapies for patients with UA/NSTEMI, with rates of 97% to 99% [10; 140]. Rates of aspirin use have been reported to be lower for older individuals and women, especially women younger than 55 years of age [18; 179].

P2Y12 Inhibitors

P2Y12 inhibitors are added to aspirin as dual-antiplatelet therapy for patients who are managed medically as well as patients treated with PCI. Three inhibitors have been approved by the U.S. Food and Drug Administration (FDA) for use in UA/NSTEMI: clopidogrel, prasugrel, and ticagrelor.

Clopidogrel

Clopidogrel was the first antiplatelet agent to become standard therapy in the ACS setting. The drug was approved by the FDA in 2002 on the basis of the findings of the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, in which 12,562 patients with UA/NSTEMI were randomly assigned to treatment with aspirin with or without clopidogrel (loading dose of 300 mg followed by 75 mg daily) and followed up for 3 to 12 months, regardless of the treatment strategy used (conservative or invasive) [180]. The risk of cardiovascular-related death, MI, or stroke was significantly lower for patients who received clopidogrel. The results were similar in many subgroups of patients.

The ACC/AHA guideline recommends clopidogrel as one of two P2Y12 inhibitors to be given in addition to aspirin to all patients (unless contraindicated) with UA/NSTEMI who are to be treated with either an early invasive or ischemia-guided strategy [3]. The recommended dose of clopidogrel is a loading dose of 300 mg or 600 mg, followed by 75 mg daily for up to 12 months. Clopidogrel is also recommended for patients who are unable to take aspirin [3].

Patient D was scheduled to go to the cardiac catheterization laboratory for a left heart catheterization and probable PCI with stent to treat an obstruction in the circumflex branch of his left coronary artery. The cardiac catheterization laboratory physician's orders specified that Patient D should receive a loading dose of 300 mg of clopidogrel on call to the catheterization laboratory. When the nurse brought the patient the medication as ordered, he commented, "I know that one. They wanted me to take it last year after my last heart attack and stent. But I couldn't afford it. That stuff is expensive!"

In today's economic climate, the cost of medications can pose a serious problem for the patient. Patients who are uninsured or underinsured can find it difficult to afford medications such as clopidogrel. Even patients with "good" insurance can find co-pay charges too high to manage on their current budget. Variations in Medicare Part D plans can create confusion and obstacles. Some drug companies may offer assistance; local hospitals may also provide assistance through resources such as charity pharmacies. Nurses are in a position to initiate discussion with the patient and family about how they plan to obtain medications after discharge and can tactfully ask if the patient has any financial issues related to obtaining prescribed medications. If the patient or family indicates a need, a case manager, discharge planner, or social worker can assess financial issues and assist patients/families to identify available resources. If a patient is unable to afford (or is unlikely to adhere to) taking clopidogrel following PCI with stent placement, the physician may choose to implant bare-metal stents (as opposed to drug-eluting stents). The different types of stents will be discussed in detail in a later section of this course.

Prasugrel

Prasugrel has been shown to be more effective than clopidogrel for patients treated with PCI with stenting. In a comparison of the two drugs in patients with moderate-to-high-risk ACS who were scheduled for PCI, prasugrel was given as a 60-mg loading dose, followed by 10 mg daily, and clopidogrel was given as a 300-mg loading dose, followed by 75 mg daily. Both drugs were given for 6 to 15 months. Prasugrel was associated with a significantly lower rate of the primary composite endpoint of cardiovascular-related death, nonfatal MI, or nonfatal stroke (9.9% vs. 12.1%) [181]. However, the risk of major bleeding was increased with prasugrel (2.4% vs. 1.8%). Overall mortality did not differ significantly between the two drugs [181].

Prasugrel has also been compared with clopidogrel in patients with UA/NSTEMI who are managed medically. In this study, prasugrel was not associated with a decrease in the primary composite endpoint of cardiovascular-related death, MI, or stroke (13.9% vs. 16%) [182]. The rates of major bleeding were similar.

The ACC/AHA guideline recommends prasugrel as one of three options for maintenance antiplatelet therapy (with aspirin) for patients who have PCI and coronary stenting. Prasugrel is not recommended for patients treated with an early-invasive or ischemia-guided strategy [3].

Monitor patients for enhanced bleeding effects if used concurrently with warfarin. Instruct patients on increased risk of bruising and bleeding with prasugrel. Due to the increased risk of bleeding, the drug should be withheld 5 to 10 days prior to any surgery or dental procedure [183].

Ticagrelor

Ticagrelor, the first in a new class of antiplatelets known as cyclopentyl-triazolo-pyrimidines, was approved by the FDA in 2011 [184]. Its mechanism of action differs from that of clopidogrel and prasugrel in that it does not require hepatic metabolism for activation and its action is reversible. Ticagrelor achieves greater and more consistent platelet inhibition than clopidogrel [184].

Ticagrelor was compared with clopidogrel in the Study of Platelet Inhibition and Patient Outcomes (PLATO), a randomized, controlled trial involving 18,624 patients, most of whom had UA/NSTEMI [185]. After 12 months, the rate of the primary composite endpoint (i.e., cardiovascular-related death, MI, or stroke) was lower in the ticagrelor and aspirin group than in the clopidogrel and aspirin group (9.8% vs. 11.7%) [185]. In addition, the all-cause death rate was lower in the ticagrelor group than in the clopidogrel group. Although the overall rates of major bleeding did not differ between the two groups, ticagrelor was associated with a higher rate of major bleeding in a subgroup of patients who did not have CABG.

The ACC/AHA guideline recommends ticagrelor as an option (with aspirin) as maintenance antiplatelet therapy for up to 12 months after initial treatment with either an early invasive or ischemia-guided strategy [3]. As a class IIaB recommendation, the ACC/AHA note a preference for ticagrelor over clopidogrel. The recommended dose is 180 mg as a loading dose, followed by 90 mg twice daily. The benefit of ticagrelor compared with clopidogrel is limited to an aspirin dose of 75–100 mg [186].

Adherence to guidelines on the use of a P2Y12 inhibitor has been low, especially for patients with UA/NSTEMI, with rates of 10% to 57% [8]. Rates of use have been lower among women [11]. In addition, some inhibitors have been used inappropriately; for example, in one study, 3% of patients with prior stroke received prasugrel despite its contraindication in that setting [8].

Glycoprotein IIb/IIIa Inhibitors

Glycoprotein IIb/IIIa inhibitors are potent inhibitors of platelet aggregation. Three intravenous glycoprotein IIb/IIIa inhibitors have been approved for clinical use: abciximab, eptifibatide, and tirofiban. Intravenous glycoprotein IIb/IIIa inhibitors are recommended, as oral agents in this class have been associated with increased risk for bleeding and mortality [3]. A meta-analysis (48 trials, 33,513 patients) demonstrated that glycoprotein IIb/IIIa inhibitors were associated with a lower all-cause mortality at 30 days after PCI but not at six months, compared with placebo or usual care [187]. The rate of severe bleeding was increased with glycoprotein IIb/IIIa inhibitors. Less benefit was found when clopidogrel was used. When glycoprotein IIb/IIIa inhibitors were used as part of initial medical treatment of UA/NSTEMI (12 trials, 33,176 patients), there was no decrease in mortality at 30 days, although the rate of death or MI was slightly lower at 30 days and six months [187]. Again, the risk of severe bleeding was higher with glycoprotein IIb/IIIa inhibitors.

The ACC/AHA guideline recommends a glycoprotein IIb/IIIa inhibitor for patients at intermediate-to-high risk (i.e., elevated troponin levels) who are to be treated with an early invasive strategy and dual-antiplatelet therapy. Eptifibatide and tirofiban are the preferred inhibitors (class IIbB) [3]. The recommended use of glycoprotein IIb/IIIa inhibitors is suboptimal in two ways. First, guideline-recommended use is low, especially among women [11; 188; 189]. Despite the clear benefit of glycoprotein IIb/IIIa inhibitors for high-risk patients, studies have shown that treatment with the drugs are directed toward patients at lower risk, with its use in high-risk patients ranging from 18% to 35% [190; 191]. Use of glycoprotein IIb/IIIa inhibitors has also been suboptimal with respect to dosing; in one study, an excess dose was given to 26.8% of patients [192]. Excess dosing was more likely among older individuals, women, and patients with renal insufficiency, diabetes, heart failure, or low body weight [192]. Increased risk of major bleeding and mortality were associated with an excess dose.

ANTICOAGULANT THERAPY

Parenteral anticoagulant therapy (in addition to antiplatelet therapy) is recommended for patients with definite or likely UA/NSTEMI, regardless of the initial treatment strategy (early invasive or ischemia-guided) [3].

The anticoagulants used in the UA/NSTEMI setting are enoxaparin, bivalirudin, fondaparinux, and unfractionated heparin [3].

Enoxaparin

Enoxaparin is a low-molecular-weight heparin that offers many pharmacologic advantages compared with unfractionated heparin [193]:

- More predictable anticoagulant effect
- Greater bioavailability
- Lower incidence of heparin-induced thrombocytopenia
- Routine monitoring not required
- Given as a fixed-weight base dose

Compared with unfractionated heparin, enoxaparin has been associated with lower rates of recurrent ischemic events and of invasive procedures in the short term, as well as at 1 year among patients with UA [194]. Among high-risk patients with UA/NSTEMI treated with an early invasive strategy, the rate of death or MI at 30 days did not differ significantly between enoxaparin and unfractionated heparin, and enoxaparin was associated with an increased risk of major bleeding [152; 195]. A 2018 systematic review and meta-analysis found similar death rates and major bleeding between enoxaparin and unfractionated heparin [196].

The ACC/AHA guideline recommends enoxaparin as an option for all patients with NSTE-ACS [3]. The recommended dose is 1 mg/kg, given subcutaneously, every 12 hours, and the drug is continued throughout the hospitalization or until PCI is done [3]. The dose should be decreased to 1 mg/kg daily for patients with a creatinine clearance less than 30 mL/min.

Studies have shown that 14% to 19% of patients with UA/NSTEMI have received an excess dose of low-molecular-weight heparin [192; 197]. A higher dose was significantly associated with major bleeding and death [197]. The patients who received excess doses were more likely to be older, smaller, and female [192; 197].

Bivalirudin

Bivalirudin is a direct thrombin inhibitor, and it has shown little benefit in lowering the risk of adverse outcomes compared with unfractionated heparin. Bivalirudin has been evaluated only in patients being considered for an early invasive strategy. In a study of 13,819 moderate- and high-risk patients, bivalirudin alone was compared with two other regimens: bivalirudin plus a glycoprotein IIb/IIIa inhibitor, and heparin (unfractionated heparin or enoxaparin) plus a glycoprotein IIb/IIIa inhibitor. Bivalirudin plus a glycoprotein IIb/IIIa inhibitor was noninferior to heparin plus a glycoprotein IIb/IIIa inhibitor with respect to composite endpoint (death, MI, or unplanned revascularization) at 30 days [198]. Bivalirudin alone was also noninferior to heparin plus a glycoprotein IIb/IIIa inhibitor, but it offered a significant benefit in terms of major bleeding [198]. At one year, there was no significant difference in the composite endpoint among the three groups [199]. A meta-analysis of 15 trials that included more than 25,000 patients undergoing PCI found that bivalirudin was associated with an increased risk of stent thrombosis, MI, all-cause mortality, and major adverse cardiac events and a reduced risk of major bleeding. When the dose of heparin in the control arm was more than 100 units/kg, bivalirudin was associated with a reduction in major bleeding; when the dose of heparin was less than 75 units/kg, bivalirudin was not associated with reduced major bleeding [200].

The ACC/AHA guideline recommends bivalirudin only for patients who are to have an early invasive strategy [3]. The recommended dose is 0.10 mg/kg as a loading dose, followed by 0.25 mg/kg/hour, to be continued until diagnostic angiography or PCI is performed [3].

Fondaparinux

Fondaparinux is a synthetic polysaccharide molecule that is a selective inhibitor of activated Factor X. It has been compared with enoxaparin in patients with NSTE-ACS and found to have similar efficacy in terms of a primary endpoint of ischemic events, but offering benefit in terms of a significantly lower rate of major bleeding [201; 202; 203]. The ACC/AHA guideline recommends fondaparinux, 2.5 mg subcutaneously daily, for the duration of hospitalization or until PCI is done [3]. When fondaparinux is used alone in this setting, an additional anticoagulant with anti-IIa activity should be given to help prevent catheter thrombosis [3].

Unfractionated Heparin

Unfractionated heparin has been used in the ACS setting since the early 1960s. Heparin prevents the formation of thrombi by accelerating the action of the proteolytic enzyme antithrombin that inactivates Factors IIa, IXa, and Xa [193]. An early meta-analysis (six trials, 1,353 patients) showed that unfractionated heparin plus aspirin reduced the risk for death or MI by 33% compared with aspirin alone among patients with UA [204]. These studies preceded the era of dual-antiplatelet therapy and early catheterization and revascularization.

The ACC/AHA guideline recommends giving unfractionated heparin for 48 hours or until PCI is performed [3]. A weight-adjusted dose is preferred to a fixed initial dose, as anticoagulation is more predictable with such dosing [3]. The recommended dose in the ACC/AHA guideline is an initial loading dose of 60 IU/kg (to a maximum of 4,000 IU) and an initial infusion of 12 IU/kg/hour (to a maximum of 1,000 IU/hour), which is adjusted to a therapeutic aPTT range [3].

CHOICE OF TREATMENT STRATEGY: EARLY INVASIVE VS. ISCHEMIA-GUIDED STRATEGY

As stated earlier, risk stratification is essential to determine the level of treatment: an early invasive or an ischemia-guided strategy. An early invasive approach involves diagnostic angiography, with revascularization performed if appropriate based on coronary anatomy [3]. The procedure is typically done within 24 hours (early invasive) or 25 to 72 hours (delayed invasive). The optimal timing of angiography has not been established [3]. With an ischemia-guided strategy (previously referred to as a conservative approach or medical management), noninvasive testing is done and angiography is performed only when testing demonstrates evidence of ischemia. The ACC/AHA guideline provides direction for appropriately selecting an early invasive or ischemia-guided strategy (***Table 10***) [3].

Early Invasive Strategy

The findings of most studies have indicated that a routine early invasive strategy is superior to an ischemia-guided strategy in terms of reducing the rate of cardiovascular-related death or MI, as well as of angina and rehospitalization [17; 205; 206]. However, a follow-up Cochrane review concluded that there was no evidence of appreciable benefit with routine invasive strategies and that a selectively invasive (conservative) strategy based on clinical risk for recurrent events is the preferred management strategy [207]. Additionally, a meta-analysis found insufficient evidence to support either approach as having a survival benefit for patients with NSTE-ACS [208]. The greatest advantage of an early invasive strategy has been found among patients at high risk.

FACTORS ASSOCIATED WITH APPROPRIATE SELECTION OF EARLY INVASIVE STRATEGY OR ISCHEMIA-GUIDED STRATEGY IN PATIENTS WITH NSTE-ACS	
Treatment Strategy	**Factors Guiding Selection**
Immediate invasive (within two hours)	Refractory angina Signs or symptoms of HF or new or worsening mitral regurgitation Hemodynamic instability Recurrent angina or ischemia at rest or with low-level activities despite intensive medical therapy Sustained VT or VF
Ischemia-guided strategy	Low-risk score (e.g., TIMI [0 or 1], GRACE [<109]) Low-risk, Tn-negative female patients Patient or clinician preference in the absence of high-risk features
Early invasive (within 24 hours)	None of the above, but GRACE risk score >140 Temporal change in Tn New or presumably new ST depression
Delayed invasive (within 25 to 72 hours)	None of the above, but diabetes mellitus Renal insufficiency (GFR <60 mL/min/1.73 m^2) Reduced LV systolic function (EF <40%) Early postinfarction angina PCI within 6 months Prior CABG GRACE risk score 109–140; TIMI score ≥2
CABG = coronary artery bypass graft; EF = ejection fraction; GFR = glomerular filtration rate; GRACE = Global Registry of Acute Coronary Events; HF = heart failure; LV = left ventricular; NSTE-ACS = non-ST-elevation acute coronary syndrome; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction; Tn = troponin; VF = ventricular fibrillation; VT = ventricular tachycardia.	
Source: [3]	*Table 10*

An urgent or immediate invasive strategy is recommended for patients with NSTE-ACS with refractory angina or hemodynamic or electrical instability who do not have serious comorbidities or contraindications [3]. An early invasive strategy is recommended for patients with NSTE-ACS who are initially stabilized and at elevated risk for clinical events [3]. The guideline recommends against an early invasive strategy for patients with acute chest pain and a low likelihood of ACS (normal troponin levels) as well as for patients with extensive comorbidities (class III: no benefit).

Ischemia-Guided Strategy

What is the objective of an ischemia-guided strategy in the management of NSTEMI?

The objective of an ischemia-guided strategy is to avoid unnecessary treatment (and associated costs) for patients at low risk for significant CHD. The ACC/AHA guideline notes that an ischemia-guided strategy may be considered for patients with NSTE-ACS who are initially stabilized and at elevated risk for clinical events (class IIbB) [3]. It is also reasonable to consider clinician and patient preference in decision making about an ischemia-guided strategy (class IIbC). Patients at low or intermediate risk who have had no ischemia at rest or with low-level activity for at least 12 to 24 hours should have noninvasive stress testing (class IB) [3].

Many factors other than risk influence the use of an early invasive strategy. Such a strategy has been used more often, regardless of patients' risk, when a cardiac catheterization laboratory is available or the treating physician is a cardiologist [190; 209; 210]. Patient demographic characteristics, such as age, race, and gender, are also factors. Data from trials indicate that an early invasive strategy is used less frequently for older patients, Black patients, and women [9; 14; 109; 206; 209; 211].

The benefit of an early invasive strategy for women is unclear [17; 206]. However, when women have high-risk features, such as elevated troponin levels, an early invasive approach does lead to better outcomes; women at low-risk have better outcomes from an ischemia-guided approach [212; 213]. These findings led the ACC/AHA to emphasize that an immediate invasive strategy should be used for women who are eligible for that approach and that an early invasive strategy should not be used for women at low risk for ACS [3].

Revascularization Procedures

CABG was once the primary revascularization procedure, but advances in less invasive techniques have contributed to a decline in CABG rates and an increase in the use of PCI for NSTE-ACS [9; 214].

A comprehensive comparison of CABG and PCI was carried out in the Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) study, and the findings were considered in the formulation of the 2011 ACC/AHA/Society for Cardiac Angiography and Interventions (SCAI) guideline recommendations for PCI [5]. In a meta-analysis (31 trials, 15,004 patients) published after the guideline, among patients eligible for either PCI or CABG, the latter procedure was associated with lower rates of repeat revascularization, and death; the rate of MI was similar, and the rate of stroke was higher with CABG [215].

Class I recommendations for the use of PCI include patients who have refractory angina or hemodynamic or electrical instability (without comorbidities or contraindications), and initially stabilized patients who have an elevated risk for clinical events [5]. PCI is preferred for patients with discrete lesions, in large-caliber vessels, or one or two vessels, whereas CABG is recommended for more extensive CHD, including left main disease, three-vessel disease, or two-vessel disease with severe involvement of the proximal left anterior descending coronary artery [6]. For patients with multivessel disease, CABG has been associated with higher adjusted rates of long-term survival and lower rates of MI and repeat vascularization compared with PCI with stenting [216; 217]. CABG is also recommended for patients with left ventricular systolic dysfunction [6].

MANAGEMENT OF VARIANT ANGINA

Which medication is prescribed in variant angina to prevent coronary vasospasm?

Patient V, a woman 45 years of age, was admitted to a general medical-surgical unit with a diagnosis of possible upper gastrointestinal bleeding. She stated that she had no known cardiac history; however, she had risk factors for CHD, including a current history of 1 to 2 packs per day smoking history and dyslipidemia for which she takes simvastatin.

Two days following admission, Patient V called the nurse complaining of extreme, severe chest pain that started while she was in the bathroom. The physician was notified and ordered cardiac biomarkers and a 12-lead ECG. Sublingual nitroglycerin tablets were administered and effectively relieved the acute chest pain. The patient's biomarkers returned negative for MI; however, her ECG during the chest pain episode showed ST-segment elevation. A follow-up ECG, taken when the pain had resolved, showed resolution of ST-segment elevation and no electrocardiographic indications of an evolving or resolving MI.

After careful assessment and evaluation of serial laboratory test, serial ECGs, physical exam findings, and other diagnostic tests, the physician determined that Patient V had variant (Prinzmetal or vasospastic) angina. Diltiazem was ordered to prevent coronary vasospasm and recurrent chest pain attacks.

The primary medical therapy for management of variant or vasospastic angina involves nitrates and calcium-channel blockers. Within minutes of administration, nitroglycerin has been found to effectively treat episodes of angina and myocardial ischemia caused by vasospasm. Long-acting nitrates can reduce the frequency of recurrent episodes of chest pain. Calcium-channel blockers, specifically nifedipine, amlodipine, verapamil, and diltiazem, are prescribed to prevent coronary vasospasm and the subsequent ischemia that can result. In this patient population, calcium-channel blockers are preferred over beta blockers [218; 219].

MANAGEMENT OF COCAINE-INDUCED ACS

Patient C presented to the emergency department with a complaint of severe substernal chest pain, radiating from the left side of his chest down his left arm. He stated that he was "very nauseated" and that his symptoms came on suddenly. The patient is 19 years of age; when questioned, he admitted that he smoked 1 to 2 packs per day but denied all other risk factors for CHD. He had no previous history of ACS or interventions for CHD, such as PCI. He appeared "jittery" and anxious and asked to leave the emergency department to smoke. His initial 12-lead ECG showed sinus tachycardia but no evidence of myocardial ischemia or infarct. His initial biomarkers showed troponin I within normal limits. Upon careful questioning by the emergency department physician, Patient C admitted that he used cocaine approximately one hour before the development of his symptoms.

The 2008 AHA statement contains several recommendations for the management of patients with cocaine-associated chest pain and MI [48]. Because cocaine use may impact treatment, patients (especially younger patients) who present with signs of possible ACS should be asked about cocaine use. Establishing that a patient does use cocaine should depend primarily upon self-reporting. However, a urine toxicology screen that measures cocaine metabolites (as well as other drug metabolites) may be indicated in patients who are young, have a history of illicit drug use, or who are unable to communicate with the healthcare team [48].

Evaluation of possible cocaine-induced chest pain in the emergency department should follow the same guidelines as the evaluation for ACS without cocaine use. Troponin levels should be monitored. Because cocaine can cause a breakdown of muscle fibers resulting in the release of myoglobin into the bloodstream, elevated myoglobin and total creatine kinase levels may be present that are not indicative of myocardial ischemia or infarct. Cardiac troponins are the biomarkers of choice to assess for a diagnosis of infarction [3; 48; 220].

Patients with cocaine-induced chest pain who show ECG and biomarker evidence of ischemia or infarct should be admitted for monitoring, observation, and further treatment as indicated. General medical therapies, similar to those used in management of non-cocaine related ACS, should be employed. In addition, the use of IV benzodiazepines as part of the early management of these patients may be indicated. In patients who use cocaine, benzodiazepines help to relieve chest pain and manage neuropsychiatric manifestations. Aspirin, calcium-channel blockers, and nitroglycerin are also recommended; beta blockers are not recommended with acute cocaine intoxication [3; 48; 220].

TREATMENT OF STEMI

Patient K, a man 59 years of age, was admitted to the hospital with a diagnosis of possible H1N1 flu. He was treated with appropriate medical therapy, and his condition improved. On the day before his expected discharge, he called the nurse and complained of a severe, stabbing pain in his chest. He was diaphoretic and complained of feeling nauseated. His blood pressure was elevated to 170/90 mm Hg, and his heart rate was 100-110 beats per minute. He rated his pain 10 out of 10 and stated the pain was located in his left chest, left arm, and back. An ECG was completed, and blood for cardiac biomarkers was obtained. The 12-lead ECG showed non-specific ST-wave changes. A serial 12-lead ECG taken 30 minutes later, however, showed ST elevation in the anterior leads. Cardiology confirmed a diagnosis of STEMI.

When an ECG demonstrates ST-segment elevation, the goal of treatment is to immediately restore normal coronary perfusion through the occluded infarct-related artery, thus decreasing ischemic time [2]. Re-establishing blood flow through the occluded artery is crucial for limiting the size of the infarct, minimizing myocardial damage, preserving left ventricular function, decreasing morbidity, and improving survival [2; 221]. Options for re-establishing normal coronary blood flow through an occluded artery include:

- PCI with or without placement of intracoronary stents
- Fibrinolytic therapy
- Combination PCI and fibrinolytic therapy
- CABG surgery

Advances in revascularization procedures and antiplatelet and anticoagulant therapies have improved outcomes for patients with STEMI, with significant decreases in the rates of mortality and morbidity [2; 222; 223]. The reported mortality rates are approximately 5% to 6% (in-hospital) and 7% to 18% (one-year) [2]. Morbidity includes heart failure, pulmonary edema, reinfarction, cardiogenic shock, and stroke, and rates of these events have also declined significantly [222].

Reperfusion therapy is the cornerstone in the management of STEMI, and antiplatelet and anticoagulant agents are necessary as ancillary therapy. The options for reperfusion include revascularization procedures and/or pharmacologic (fibrinolytic) therapy. As with the treatment for NSTEMI, the use of PCI has become the primary approach to revascularization; approximately 80% to 90% of patients have PCI revascularization based on angiographic findings [224]. In addition, PCI is the preferred strategy for reperfusion because of its superior outcomes compared with fibrinolytic therapy [2; 224]. However, gaining the optimal benefit from PCI depends on many factors, and timing is the most important variable in selecting a reperfusion therapy [2; 221]. Care should also be taken to evaluate patients for contraindications to fibrinolytic therapy [5].

The ACCF/AHA guideline on the management of STEMI was most recently updated in 2013. The guideline notes that patients with STEMI should be treated in either a coronary care unit or a stepdown unit [2]. Care provided in a coronary care unit should be structured according to evidence-based protocols, and nursing staff should be certified in critical care. Patients who are admitted to a coronary care unit may be transferred to a stepdown unit once they have been clinically stable for 12 to 24 hours [2]. Low-risk patients who have had successful PCI may be admitted directly to a stepdown unit.

TIMING

A familiar adage associated with STEMI is "time is muscle," and every effort should be made to shorten the ischemic time as much as possible. The timing of reperfusion therapy is a complex issue involving the time from the onset of symptoms and the time from presentation to treatment. The time for transfer to another hospital is also a factor for most patients, as most hospitals do not have a cardiac catheterization laboratory and a skilled, readily available PCI team.

The 2013 ACCF/AHA guideline indicates that PCI is preferred over fibrinolytic therapy for patients with STEMI when it can be performed in a timely manner by experienced operators [2]. PCI should be done within less than 90 minutes after the patient's arrival at the emergency department (door-to-device time) [2]. If PCI cannot be done within 90 minutes, fibrinolytic therapy should be initiated as the reperfusion strategy within 120 minutes of the first medical contact.

EVIDENCE-BASED PRACTICE RECOMMENDATION

As a systems goal, EMS transport directly to a PCI-capable hospital for primary PCI is the recommended triage strategy for patients with STEMI, with an ideal first medical contact-to-device time system goal of 90 minutes or less.

(https://www.ahajournals.org/doi/10.1161/CIR.0b013e3182742c84. Last accessed January 10, 2022.)

Strength of Recommendation/Level of Evidence: IB (Procedure/treatment should be performed based on data derived from a single randomized clinical trial or nonrandomized studies evaluating limited populations.)

The most significant factor in achieving an optimal outcome from PCI is timing. Findings from hospitals reporting to the Centers for Medicare and Medicaid Services have shown an improvement in the number of patients treated with primary PCI within the recommended 90-minute window, from 44.2% in 2005 to 91.4% in 2010 [225]. In addition, the median door-to-balloon or door-to-device time declined from 96 minutes in 2005 to 64 minutes in 2010 [225].

Improvements in door-to-balloon time have been attributed to national initiatives focused on identification of barriers to appropriate care and implementation of innovative protocols. For example, a quality improvement campaign called Door-to-Balloon (D2B) Alliance for Quality, launched by the ACC, has made it possible for patients experiencing STEMI anywhere in the United States to receive lifesaving reperfusion in less than 90 minutes and often in less than 60 minutes [226]. These initiatives successfully addressed physician and organizational barriers with efforts to develop systems of care that increase patient access to primary PCI based on whether the patient presents to a PCI-capable or non-capable facility [2].

Strategies to Improve Timing of Therapy

Specific strategies that have improved the door-to-device time interval focus on three key components: door-to-ECG time, ECG-to-catheterization laboratory time, and laboratory arrival-to-device time. The ACCF/AHA provides the following steps as a general protocol in improving door-to-device times [2]:

- A prehospital ECG to diagnose STEMI is used to activate the PCI team while the patient is en route to the hospital.
- Emergency physicians activate the PCI team.
- A single call to a central page operator activates the PCI team.
- A goal is set for the PCI team to arrive in the catheterization laboratory within 20 minutes after being paged.
- Timely data feedback and analysis are provided to members of the STEMI care team.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Reperfusion therapy is reasonable for patients with STEMI and symptom onset within the prior 12 to 24 hours who have clinical and/or ECG evidence of ongoing ischemia. Primary PCI is the preferred strategy in this population.

(https://www.ahajournals.org/doi/10.1161/CIR.0b013e3182742c84. Last accessed January 10, 2022.)

Strength of Recommendation/Level of Evidence: IIaB (It is reasonable to perform the procedure based on data derived from a single randomized clinical trial or nonrandomized studies evaluating limited populations.)

PCI

PCI is an invasive procedure performed in the cardiac catheterization laboratory by a highly skilled, trained team. In the treatment of STEMI, the goal is to open the occlusion in the infarct-related vessel, restoring blood flow and oxygen supply. As noted, PCI has become more commonly used than CABG for revascularization. PCI for STEMI can be subcategorized according to when the procedure is done and whether it is done in conjunction with fibrinolytic therapy. Primary PCI refers to PCI that is done alone as primary treatment after diagnostic angiography [2]. (As will be described, ancillary treatment with anticoagulant and antiplatelet agents should be given to support PCI.) Facilitated PCI was once a strategy of full- or half-dose fibrinolysis (with or without glycoprotein IIb/IIIa inhibitors) and immediate transfer for planned PCI within 90 to 120 minutes [2]. However, no net clinical benefit has been found with this strategy, and it is not recommended [2]. Rescue PCI refers to transfer for PCI after fibrinolysis has failed. A pharmacoinvasive strategy is the administration of fibrinolytic therapy, in either the prehospital setting or at a non-PCI-capable hospital for early coronary angiography and PCI when appropriate [2].

PCI encompasses a variety of procedures that may be used to restore blood flow through an occluded artery. These procedures include percutaneous transluminal coronary angioplasty, or balloon angioplasty, and angioplasty with placement of one or more intracoronary stents. In PCI, a slender balloon-tipped catheter is inserted through an artery in the groin to the area of blockage in the coronary artery. Once in position, the balloon is inflated, compressing the plaque and dilating the narrowed coronary artery so that blood can flow more easily [33; 34].

To maintain patency in the newly re-opened artery, intracoronary stents may be deployed. Best described as a wire metal-mesh tube, an intracoronary stent is carried by a balloon catheter to the area of the blockage. When the balloon is inflated, the stent expands and locks in place against the vessel wall, keeping the lumen of the vessel open. Blood flow to the affected area of the heart is restored, and myocardial ischemia is relieved. The stent stays in the artery permanently. Within a few weeks of the time a stent is placed, the endothelium of the artery grows over the metal surface of the stent [33; 34].

Following stent placement, occlusions may develop in a stent or near the junction between the end of a stent and the native vessel. To combat this issue, researchers developed a new type of stent called a drug-eluting stent; these stents are coated with medications that reduce inflammation and thrombus formation, thereby reducing the risk of restenosis at the site of the stent. Stents not coated with drugs are called bare-metal stents. Not all occlusions or all vessels are amenable to balloon dilatation or deployment of stents. In some cases, the degree of coronary occlusion is too great to be re-opened through percutaneous means. Coronary artery bypass surgery may be indicated in these cases. PCI also cannot be performed on smaller vessels that branch off from the major arteries; the lumens in these vessels are too small to permit safe passage of the catheter [33; 34].

Primary PCI

Primary PCI is preferred because of the many advantages it offers compared with fibrinolytic therapy, including wider eligibility, better rates of reperfusion, lower risks, and improved outcomes [100; 224; 227]. PCI is especially preferred for high-risk patients, specifically patients 75 years of age and older, patients with an unclear diagnosis, and patients with cardiogenic shock, heart failure, or ventricular arrhythmias [2]. However, analysis of data has shown that PCI has been done less often among patients at high risk (41%) than among patients at low risk (60%) or intermediate risk (54%) [190].

Class I indications for primary PCI include the following [5]:

- STEMI symptoms within 12 hours (level A)
- Severe heart failure or cardiogenic shock (level B)
- Contraindications to fibrinolytic therapy with ischemic symptoms less than 12 hours (level B)

The ACC/AHA guideline notes that PCI is reasonable for patients with clinical and/or ECG evidence of ongoing ischemia 12 to 24 hours after onset of symptoms (class IIaB) and might be considered for asymptomatic patients with STEMI and higher risk who presented between 12 and 24 hours after the onset of symptoms (class IIbC) [5].

The use of coronary stents during PCI reduces the rates of adverse events such as reocclusion, restenosis, and target-vessel revascularization [5; 100; 224]. Drug-eluting stents have been associated with lower long-term rates of target-vessel revascularization and restenosis compared with bare-metal stents, but the reduction has varied among the many types of drug-eluting stents and stent thrombosis was originally a complication [228; 229]. Subsequent-generation drug-eluting stents were developed to overcome this complication, and thin-strut fluoropolymer-coated cobalt chromium everolimus-eluting stents have been associated with rates of stent thrombosis that are lower than those for other types of drug-eluting stents or bare-metal stents [230]. The first of the subsequent-generation stents were designed to compensate for the insufficient radial strength of the polymer materials, which resulted in higher thrombosis rates than conventional drug-eluting stents. Newer-generation stents have improved structural design, postprocessing of bioresorbable polymer materials, or altering bioresorbable metallic alloys [231; 232].

The complications of primary PCI include adverse reactions to the contrast medium, volume loading, difficulty with arterial access, and technical complications [100]. Reperfusion injury and hemorrhagic transformation of a bland infarction and hemorrhagic stroke are rare after primary PCI [224].

Primary PCI is supported by antiplatelet and antithrombin therapy. Class I recommendations for this therapy in patients with STEMI include the following [5]:

- Aspirin (level B)
- P2Y12 inhibitors (level A)
- Unfractionated heparin (level C)
- Bivalirudin (level B)

The aspirin dose before PCI should be 325 mg for patients who had not been taking aspirin therapy and 81–325 mg for patients who had already been taking daily aspirin [5]. If stents are to be implanted during PCI, a loading dose of a P2Y12 inhibitor should be given (clopidogrel, 600 mg; prasugrel, 60 mg; or ticagrelor, 180 mg) [5]. For clopidogrel, a 300-mg loading dose is recommended for patients who have PCI within 24 hours after receiving fibrinolytic therapy; a 600-mg loading dose is recommended for patients who have PCI more than 24 hours after receiving fibrinolytic therapy [5]. This recommendation is based on the results of several investigations to explore various loading doses of clopidogrel before or during PCI. A meta-analysis of seven studies demonstrated that a 600 mg loading of clopidogrel reduces the rate of adverse cardiovascular events without an increase in major bleeding compared with 300 mg [5]. The findings of another study suggested that a 600-mg loading dose (compared with a 300-mg dose) is associated with improvements in procedural angiographic endpoints and one-year clinical outcomes in patients with STEMI who undergo primary PCI [5]. No benefit is derived from increasing the loading dose to 900 mg compared with 600 mg. The guideline acknowledges that the safety and efficacy of pretreatment with clopidogrel remains controversial [5].

When compared with clopidogrel, prasugrel was associated with a 2.2% reduction in a composite endpoint of cardiovascular-related death, nonfatal reinfarction, or nonfatal stroke [5]. Prasugrel is contraindicated in patients with active pathologic bleeding or history of transient ischemia attack or stroke. Its use is not recommended for patients older than 75 years of age because of increased risk of fatal intracranial bleeding [5].

If unfractionated heparin is used, it is reasonable to give a glycoprotein IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-bolus tirofiban), regardless of whether patients are pretreated with clopidogrel [5]. The ACCF/AHA guideline for STEMI states that it is reasonable to begin treatment with abciximab before or at the time of primary PCI (with or without stenting) [2]. The precise timing of administration has not been defined. Treatment with tirofiban or eptifibatide may also be considered at the time of primary PCI [2].

It may be reasonable to administer intravenous glycoprotein IIb/IIIa receptor antagonist in the precatheterization laboratory setting (e.g., ambulance, emergency department) to patients with STEMI for whom primary PCI is intended.

(https://www.ahajournals.org/doi/10.1161/CIR.0b013e3182742c84. Last accessed January 10, 2022.)

Strength of Recommendation/Level of Evidence: IB (Procedure/treatment should be performed based on data derived from a single randomized clinical trial or nonrandomized studies evaluating limited populations.)

With regard to anticoagulant therapy, unfractionated heparin is recommended but should not be given to patients already receiving therapeutic enoxaparin (subcutaneously) (class III: harm) [5]. Bivalirudin is also a recommended anticoagulant, with or without previous treatment with unfractionated heparin (class IB) [5]. Bivalirudin or argatroban should be used instead of unfractionated heparin in patients with heparin-induced thrombocytopenia (class IB). Fondaparinux should not be used as the only anticoagulant with PCI (class III) [5]. An additional anticoagulant with anti-Ha activity should be used because of the risk of catheter thrombosis.

Upon further questioning, Patient K reported a history of CHD with stent placement 5 years previously and CABG surgery 10 years previously. The medical team determined that primary PCI was indicated to open the occluded, infarct-related vessel. While awaiting the start of the procedure, Patient K received aspirin 325 mg and 600 mg of clopidogrel. He also received a bolus of abciximab, and a continuous infusion was started.

Post-PCI Assessment and Monitoring

What is an early sign of a retroperitoneal bleed following PCI?

Monitoring the patient closely for complications and signs of recurrent ischemia is particularly important in the 24-hour period following reperfusion with PCI. Complications may include bleeding, formation of clot or obstruction, drop in platelet count, reocclusion, renal failure, and cerebrovascular accident [34; 233].

After PCI for STEMI, aspirin should be continued indefinitely.

(https://www.ahajournals.org/doi/10.1161/CIR.0b013e3182742c84. Last accessed January 10, 2022.)

Strength of Recommendation/Level of Evidence: IA (Procedure/treatment should be performed based on data derived from multiple randomized clinical trials or meta-analyses evaluating multiple populations.)

Bleeding may occur from the arterial puncture site. Initial indications include frank bleeding from the puncture site and/or development of a hematoma in the area surrounding the site. A retroperitoneal bleed may also occur; an early sign is a complaint of severe flank pain. To reduce the likelihood of bleeding, the patient should be maintained on bed rest as specified by physician orders. The length of time bed rest is indicated depends on the method used to close the arterial puncture site. The arterial puncture site, often the femoral artery, should be monitored frequently for signs of bleeding or hematoma formation [34; 233].

Formation of a clot at the puncture site reduces distal arterial blood flow and can result in signs of peripheral ischemia below the site. Indications include loss of or decrease in the peripheral pulse distal to the arterial puncture site and change in color or temperature of the distal extremity. The peripheral pulse distant to the site should be checked frequently with vital signs and arterial site checks [34; 233].

A significant drop in platelet count may be caused by an allergy or intolerance to infusing glycoprotein IIb/IIIa inhibitors. With a drop in platelet count, the patient's risk of bleeding increases. Patients receiving glycoprotein IIb/IIIa inhibitors should have a complete blood count checked at designated intervals to make sure that platelet counts are not dropping. Parameters should include orders to notify the physician if the platelet count drops below a specified level. If a patient develops a significant drop in platelet count, the infusion of the glycoprotein IIb/IIIa inhibitor is discontinued and the patient is placed on bleeding precautions and observed carefully for any signs of bleeding [34; 233].

Abrupt reocclusion of the infarct-related artery can occur within hours of the original procedure. A thrombus may form in the newly placed stent, occluding blood flow and causing symptoms of myocardial ischemia or infarct. Clinical indications include the recurrence of severe chest pain. This chest pain may be similar or worse than the patient's initial chest pain. ECG changes indicative of acute ischemia or infarct may appear. Cardiac biomarkers may trend upward. The treatment of choice is an emergent return to the cardiac catheterization laboratory for direct visualization of the vessels and possible removal of a thrombus in or near the newly placed stent. Cardiac biomarkers should be monitored post-PCI. Troponin levels that fall from previously high levels are indicative of restored perfusion; levels that initially drop then trend upward again are concerning for possible recurrent damage. Continuous ECG monitoring should also be maintained. If only 2 or 3 leads can be monitored continuously, the leads selected for monitoring should be the ones most likely to reflect any recurrent ST-segment changes [34; 233].

Renal failure can develop from the kidneys' response to the dye load administered during cardiac catheterization. Postprocedure orders may include administration of IV fluids to help to "flush" the dye through the kidneys. Adequate intake of fluids should be provided as well. Monitoring intake and output and renal function studies is indicated postprocedure [34; 233].

During PCI, it is possible for parts of plaque to break off and travel, lodging in cerebral circulation. Patients should be monitored for any change in mental status or abrupt development of any transient ischemic attack-like symptoms [34; 233].

Patient K underwent successful PCI to a branch of his circumflex artery, with placement of a drug-eluting stent. Following the procedure, he was transferred to the coronary care unit for observation and monitoring. He was placed on continuous ECG monitoring, which assessed ST-segment changes in the most appropriate leads. Vital signs were checked frequently, and the right femoral site and right pedal pulse were assessed for bleeding, signs of hematoma, or disrupted circulation. The patient remained on bed rest per orders. Laboratory tests were sent at prescribed intervals to monitor cardiac biomarkers and complete blood count. Patient K was also monitored for signs of recurrent ischemia, including recurrent chest pain and recurrent or new ST-wave changes.

Patient K recovered from the PCI. During the postprocedure period, it was noted that his groin site was dry, with no evidence of bleeding or hematoma. His pedal pulse remained strong and readily palpable. His vital signs were stable. The blood pressure measurement remained around 130 mm Hg systolic, and the patient remained chest pain free. ECG showed no further ischemic changes. His initial post-PCI complete blood count showed a slight drop in platelet count, and the initial post-PCI biomarkers showed his elevated levels starting to trend down. The follow-up laboratory results eight hours later showed his platelet count unchanged and his biomarkers continuing to trend downward. Patient K was discharged uneventfully 24 hours later.

FIBRINOLYTIC THERAPY

Sometimes referred to as "clot-busting drugs," fibrinolytic agents have the potential to open an infarct-related vessel by dissolving existing thrombi. Fibrinolytic agents degrade fibrin clots by converting plasminogen to plasmin. The benefit of fibrinolytic therapy is its potential to establish reperfusion quickly. Re-establishment of coronary blood flow within the first 30 minutes after occlusion can abort infarction [234]. Reperfusion within 30 minutes to 2 hours can salvage myocardial tissue substantially, and fibrinolytic therapy administered within this timeframe has reduced mortality [235].

Although the focus of treatment for patients presenting with STEMI is often given to PCI, fibrinolytic therapy is the treatment of choice for some patients. If a patient arrives at or is transported by EMS to a non-PCI-capable facility, the decision whether to immediately transfer to a PCI-capable facility or administer fibrinolytic therapy must be made. Factors that affect this decision include the time from onset of symptoms, the risk of complications related to STEMI, the risk of bleeding with fibrinolysis, the presence of shock or severe heart failure, and the time required for transfer to a PCI-capable hospital. The ACCF/AHA guideline recommends that, in the absence of contraindications, fibrinolytic therapy should be given to patients with STEMI and onset of ischemic symptoms within the previous 12 hours when it is anticipated that primary PCI cannot be performed within 120 minutes of first medical contact [2].

Prehospital fibrinolytic therapy may reduce the time delay from symptom onset to treatment and can be administered by a trained EMS unit either with a physician on board or with a hospital-based physician in direct contact. A meta-analysis (six randomized controlled trials) showed a 60-minute reduction in time from symptom onset to treatment with prehospital compared to hospital-based initiation of fibrinolytic therapy [236]. Data from several trials indicate that prehospital fibrinolytic therapy may lower STEMI mortality rates and is considered to be of particular benefit in rural areas [236].

Four fibrinolytic agents have been evaluated and approved in the STEMI setting: tenecteplase, reteplase, alteplase (tPA), and streptokinase (***Table 11***) [2]. Of these agents, only streptokinase is non-fibrin-specific, and a fibrin-specific agent is preferred [2]. Each agent is associated with risks and benefits, and the choice of an agent is based on several factors, including preferences in the hospital formulary, cost, ease of administration, and the possibility of subsequent PCI. Although streptokinase is the least expensive agent, it is rarely used and no longer marketed in the United States because it has been shown to be less effective than the other three drugs [2].

Alteplase is inconvenient to administer, as it must be given as an initial intravenous bolus over 30 minutes followed by 60 minutes of infusion [2; 237]. Reteplase and tenecteplase have both been compared with alteplase. Both have resulted

COMPARISON OF FIBRINOLYTIC AGENTS FOR TREATMENT OF STEMI				
Characteristic	**Streptokinase**	**Alteplase**	**Reteplase**	**Tenecteplase**
Dose	1.5 MU	Up to 100 mg	10 U + 10 U	30–50 mg
Administration	Infusion (over 30 to 60 minutes)	Bolus and infusion (over 90 minutes)	Bolus (over 2 minutes) given 30 minutes apart	Bolus
Weight-based dosing	No	Yes	No	Yes
Antigenic	Yes	No	No	No
Patency rate[a]	60% to 68%	73% to 84%	84%	85%
Fibrin specificity[b]	No	Yes (++)	Yes (++)	Yes (++++)
[a]90-minute grade 2 or 3 TIMI blood flow. [b]++++ is stronger than ++. TIMI = Thrombolysis in Myocardial Infarction.				
Source: [2]				*Table 11*

in similar mortality as alteplase, and reteplase has led to better total patency rates or complete perfusion. [238; 239; 240]. TIMI 3 flow at 90 minutes has been similar for tenecteplase and alteplase [241]. The use of alteplase has thus declined because of the availability of these more convenient drugs with similar or improved outcomes [237].

The most common complication of fibrinolytic therapy is major bleeding, which occurs in approximately 5% to 6% of patients [221]. According to one systematic review and meta-analysis, tenecteplase-based regimens are associated with lower risk of major bleeding compared with other regimens [242]. Adverse outcomes after fibrinolytic therapy are generally more common among women and older patients [240; 243]. Many instances of bleeding can be traced to incorrect dosing, particularly with weight-based agents [237]. In addition, patients who receive an improperly high dose of fibrinolytic agents have increased 30-day mortality.

Repeat fibrinolytic therapy after failed fibrinolytic therapy has not led to significant clinical improvement in terms of all-cause mortality or nonfatal reinfarction and has been associated with an increased risk for bleeding [244]. Rescue PCI is the preferred strategy for failed fibrinolytic therapy, as it has been shown to offer benefit when compared with repeat fibrinolytic therapy [244; 245; 246; 247].

Contraindications to Fibrinolytic Therapy

What is an absolute contraindication to fibrinolytic therapy?

Another factor in selecting a reperfusion approach is whether the patient has contraindications to fibrinolytic therapy. Regardless of timing, PCI should be strongly considered for patients who are at high risk for bleeding complications, especially intracranial hemorrhage. There are several absolute and relative contraindications to fibrinolytic therapy; absolute contraindications include a history of intracranial hemorrhage or of substantial closed head or facial trauma within the past 3 months, suspected aortic dissection, or active bleeding (***Table 12***) [2]. Relative contraindications include history of poorly controlled hypertension, recent internal bleeding, and oral anticoagulant therapy [2].

Nursing Assessment and Monitoring

Immediately following reperfusion with fibrinolytics, the patient is at risk to develop serious bleeding episodes or to reocclude the infarct-related vessel [34; 227]. Nursing assessment during this period is crucial and should include [34]:

- Continuous ECG monitoring for rate, rhythm, or reoccurrence of signs of acute ischemia, development of life-threatening arrhythmias
- Assessment for reoccurrence of chest pain or other symptoms associated with an acute ischemic episode
- Frequent vital sign monitoring for hypotension, drop in oxygen saturation, or other signs indicative of developing heart failure
- Assessment for any changes in level of consciousness
- Assessment for indications of bleeding

In addition, explanations about the patient's care and progress should be provided to the patient and the patient's family.

Ancillary Therapy Following Thrombolytic Therapy

As described, a STEMI-associated thrombus consists of a fibrin-rich core and a platelet-rich cap. Because of this, both antiplatelet and anticoagulant therapies play important roles in supporting reperfusion therapy by helping to maintain patency of the infarct-related artery and preventing reocclusion [2].

CONTRAINDICATIONS AND CAUTIONS FOR FIBRINOLYSIS USE IN ST-ELEVATION MYOCARDIAL INFARCTION (STEMI)[a]
Absolute Contraindications
Any prior intracranial hemorrhage
Known structural cerebral vascular lesion (e.g., arteriovenous malformation)
Known malignant intracranial neoplasm (primary or metastatic)
Ischemic stroke within three months EXCEPT acute ischemic stroke within 4.5 hours
Suspected aortic dissection
Active bleeding or bleeding diathesis (excluding menses)
Significant closed-head or facial trauma within three months
Intracranial or intraspinal surgery within two months
Severe uncontrolled hypertension (unresponsive to emergency therapy)
For streptokinase, prior treatment within the previous six months
Relative Contraindications
History of chronic, severe, poorly controlled hypertension
Substantial hypertension on presentation (systolic greater than 180 mm Hg or diastolic greater than 110 mm Hg)
History of prior ischemic stroke (greater than three months)
Dementia
Known intracranial pathology not covered in absolute contraindications
Traumatic or prolonged (greater than 10 minutes) CPR
Major surgery (within less than three weeks)
Recent (within two to four weeks) internal bleeding
Noncompressible vascular punctures
Pregnancy
Active peptic ulcer
Oral anticoagulant therapy
[a]Viewed as advisory for clinical decision making and may not be all-inclusive or definitive. INR = international normalization ratio; CPR = cardiopulmonary resuscitation.
Source: [2] *Table 12*

Clopidogrel and Aspirin

Recommended antiplatelet therapy has traditionally involved aspirin and clopidogrel. Both the 2013 ACCF/AHA guideline for STEMI and the 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy include a recommendation for clopidogrel (75 mg per day for at least 14 days and up to one year) to be added to aspirin (81 mg/day [range, 75–100 mg]) for patients with STEMI, regardless of whether reperfusion with fibrinolytic therapy has been initiated [2; 248]. Although prasugrel has been approved by the FDA for use in patients with STEMI and may be incorporated into the supportive treatment of these patients in place of clopidogrel, it is no longer recommended for use as an adjunct to fibrinolytic therapy [2; 248].

Glycoprotein IIb/IIIa Inhibitor

A glycoprotein IIb/IIIa inhibitor may also be considered as an ancillary agent for patients who receive fibrinolytic therapy. The 2013 ACCF/AHA guideline for STEMI notes that the use of a glycoprotein IIb/IIIa inhibitor (abciximab, tirofiban, or eptifibatide) is reasonable at the time of primary PCI for selected patients with STEMI; routine use is not recommended [2].

Three meta-analyses of randomized trials that support this recommendation involved a comparison of glycoprotein IIb/IIIa inhibitors in patients with STEMI who had primary PCI. In each case, there was no significant difference in 30-day mortality, reinfarction, TIMI flow grade 3, or ST-segment resolution among the agents [249; 250; 251].

Heparin, Fondaparinux, Enoxaparin, or Bivalirudin

Anticoagulant therapy is associated with bleeding complications, so care must be taken in selecting an appropriate agent, with attention paid to the patient's renal function status, the time to an invasive procedure, and overall bleeding risk [252]. Unfractionated heparin, enoxaparin, and fondaparinux are the recommended anticoagulant agents based on studies demonstrating their efficacy [2]. The 2013 ACCF/AHA guideline

IN-HOSPITAL MORTALITY RATES FOR PATIENTS WITH ST-ELEVATION MYOCARDIAL INFARCTION (STEMI) BASED ON REPERFUSION THERAPY STATUS		
Population	**No Reperfusion**	**Reperfusion**
TIMI 9 (1994)	18.9%	10.5%/7.6%[a]
NRMI (2000–2003)		
All patients	14.9%	5.7%
Women	17.9%	9.3%
Older patients (>65 years of age)	18.9%	10.5%
[a]Reperfusion with percutaneous coronary intervention/fibrinolytic therapy. TIMI = Thrombolysis in Myocardial Infarction; NRMI = National Registry of Myocardial Infarction.		
Source: [235; 255; 256]		*Table 13*

recommends bivalirudin as an acceptable anticoagulant for primary PCI or for patients undergoing rescue PCI for failed fibrinolysis. Bivalirudin may be useful as a supportive measure for patients undergoing PCI either with or without prior treatment with unfractionated heparin and is particularly useful if patients develop heparin-induced thrombocytopenia and still require anticoagulation [2]. Anticoagulation should be continued for the duration of the index hospitalization (up to eight days) or until revascularization. Enoxaparin is recommended over unfractionated heparin when anticoagulant therapy will extend beyond 48 hours [2].

Unfractionated heparin should be used for patients with severe impairment of renal function, and unfractionated heparin or enoxaparin may be used for patients who are at increased risk of bleeding and who are likely to have early angiography [252]. Researchers reviewed data on 20,479 patients to compare outcomes for unfractionated heparin and enoxaparin [253]. Significantly fewer patients in the enoxaparin group had subsequent PCI within 30 days after fibrinolytic therapy [253]. There were no differences between the two agents with respect to major bleeding in this study, whereas a 2012 meta-analysis found enoxaparin to be superior to unfractionated heparin in reducing the incidence of major bleeding [254].

Fondaparinux may also provide benefit for patients who receive fibrinolytic therapy [252]. In one trial, 12,092 patients with STEMI were randomly assigned to fondaparinux (2.5 mg once daily for up to eight days) or to placebo. Analysis of a subgroup of 5,436 patients who received fibrinolytic therapy (primarily streptokinase) showed that fondaparinux was associated with significantly lower rates of death or nonfatal MI at 30 days and severe bleeding, yielding a significant overall benefit [252]. As noted, an additional anticoagulant (with anti-IIa activity) should be used in addition to fondaparinux when PCI is to be done after fibrinolytic therapy, and fondaparinux should not be used when creatinine clearance is less than 30 mL/min [2].

NO REPERFUSION THERAPY

Despite the clear benefit of reperfusion, a significant percentage of eligible patients with STEMI do not receive reperfusion therapy and some are mistakenly considered "ineligible" [221; 222; 235; 255]. One study of 8,578 STEMI patients found that more than 7% of all individuals with no contraindications to reperfusion were not given fibrinolysis or PCI [256]. Patients who are less likely to receive reperfusion therapy are older than 65 years of age, are female, have an atypical clinical presentation, and have a history of cardiovascular disease [221; 256; 257]. Another study found that 45% of eligible patients with diabetes on dialysis were not treated with reperfusion because they were mistakenly considered ineligible [2]. Compared with in-hospital mortality rates for patients who do receive therapy, the mortality rates are substantially higher for patients who are eligible for reperfusion but do not receive it, and rates have been higher and more discrepant for women, older patients, and patients with prior congestive heart failure, MI, or CABG surgery (***Table 13***) [235; 255; 256; 258].

Patients with no contraindications to reperfusion should be selected for primary PCI or fibrinolysis. Patients who lack access to PCI or have absolute contraindications to fibrinolysis should receive antithrombotic therapy in the hope of restoring TIMI grade 3 flow to the occluded vessel and preventing complications [150]. Older ACC/AHA guidelines for STEMI included recommendations for the treatment of patients who do not receive reperfusion therapy, including administration of aspirin, clopidogrel, and anticoagulants (low-molecular-weight heparin or fondaparinux rather than unfractionated heparin) to be given for the duration of hospitalization [259]. The 2013 guideline for STEMI does not include a specific recommendation for the treatment of patients who do not receive reperfusion therapy [2]. Despite this, it may be reasonable to administer the additional recommended medications (in the absence of contraindications) in these patients [248].

Acting on the theory that late revascularization of an infarct-related artery may improve left ventricular function and survival, some researchers have explored the value of late PCI for patients who have not had reperfusion therapy. However, the results of such studies have shown that elective PCI of an occluded infarct-related artery 3 to 28 days after MI offered no incremental benefit (beyond optimal medical therapy) for stable patients. The ACCF/AHA guideline for STEMI includes a recommendation that PCI of a totally occluded infarct-related artery more than 24 hours after STEMI should not be done in asymptomatic, stable patients with one- or two-vessel disease [2].

CORONARY ARTERY BYPASS GRAFT SURGERY

Although PCI is performed more frequently, several situations call for the use of CABG. The ACCF/AHA guideline for STEMI and the ACC/AHA guideline for CABG surgery recommend emergent or urgent CABG when PCI has failed, for coronary anatomy not amenable to PCI, and at the time of surgical repair of a mechanical defect (e.g., ventricular septal, papillary muscle, free-wall rupture) [2; 6].

Emergency CABG is recommended in patients with acute MI in whom 1) primary percutaneous coronary intervention has failed or cannot be performed, 2) coronary anatomy is suitable for CABG, and 3) persistent ischemia of a significant area of myocardium at rest and/or hemodynamic instability refractory to nonsurgical therapy is present.

(https://www.ahajournals.org/doi/full/10.1161/cir.0b013e31823c074e. Last accessed January 10, 2022.)

Strength of Recommendation/Level of Evidence: IB (Procedure/treatment should be performed based on data derived from a single randomized clinical trial or nonrandomized studies evaluating limited populations.)

CABG results in a longer average recovery time and hospital stay compared with PCI (9.2 days and 3.2 days, respectively), and the in-hospital mortality is higher for CABG than for PCI (5.0% to 6.0% and 3.0% to 3.5%, respectively) [258]. However, long-term outcomes, including survival, have been similar for the two procedures. The mortality risk associated with emergent or urgent CABG is greater than that for elective CABG [100]. In addition, there is an increased risk of bleeding associated with clopidogrel and prasugrel given within five to seven days before CABG [100]. Thus, when CABG is planned, clopidogrel should be withheld for at least five days (seven days for prasugrel) unless the urgency for the procedure outweighs the increased risk for bleeding [2; 6]. P2Y12 inhibitor therapy should be resumed postoperatively [248]. The use of CABG should follow the ACC/AHA guideline for this procedure [5].

NONINVASIVE TESTING

Exercise testing in patients with STEMI is useful for risk stratification and assessment of functional capacity and should be performed to assess the presence and extent of inducible ischemia in patients who have not had angiography and do not have high-risk features [2]. The optimum time to exercise testing after STEMI has not been clearly defined. Exercise testing before discharge can provide reassurance to patients about their functional capacity and can also be used to establish exercise parameters for cardiac rehabilitation [2]. On the other hand, deferring exercise testing until three weeks after discharge in clinically low-risk patients appears to be safe and reasonable [2]. The ACCF/AHA guideline for STEMI suggests that exercise testing should be done before discharge in patients who may be candidates for a revascularization procedure and who have not undergone coronary angiography [2]. The use of exercise testing and the interpretation of its results should follow the guideline developed for this modality [154].

Echocardiography is also recommended for assessing left ventricular function in patients with STEMI who have not had coronary angiography and can be useful for evaluation of right ventricular infarction in patients with inferior STEMI and initial nondiagnostic findings [2]. Patients who have baseline abnormalities that may compromise interpretation of the ECG findings should have stress echocardiography (or myocardial perfusion imaging) to assess inducible ischemia [2]. Echocardiography and stress echocardiography should be performed according to guidelines or criteria developed for their use [260].

GENERAL CARE AND ADJUVANT THERAPIES

In addition to either catheter-based or pharmacologic reperfusion, treatment of patients with STEMI involves the use of some of the same general care principles (such as those regarding bed rest and the use of oxygen) and drugs as those recommended for patients with NSTE-ACS. Adjuvant therapy involves the use of dual-antiplatelet therapy, nitroglycerin, morphine, beta blockers, ACE inhibitors, calcium-channel blockers, and statins; the drugs used depend on whether the patient is treated with PCI or fibrinolytic agents [2].

Antiplatelet Therapy

The 2013 ACCF/AHA guideline for the management of STEMI recommends aspirin at a dose of 162–325 mg as a loading dose before either PCI or fibrinolytic therapy [2]. A P2Y12 inhibitor is used along with aspirin as dual-antiplatelet therapy. For patients treated with PCI, clopidogrel (600 mg), prasugrel (60 mg), or ticagrelor (180 mg) should be given as a loading dose as early as possible or at the time of the PCI [2]. Treatment with a P2Y12 inhibitor is continued for one year. Clopidogrel is the recommended P2Y12 inhibitor to support fibrinolytic therapy; a loading dose of 300 mg is used for patients 75 years of age or younger, and no loading dose is used for patients older than 75 years of age [2]. Treatment with clopidogrel is continued for at least 14 days and up to one year.

Nitroglycerin/Morphine

What is the drug of choice to manage pain associated with STEMI?

The benefit of nitroglycerin for patients with STEMI has been modest, but the drug can be given sublingually (0.4 mg every five minutes up to three doses) for persistent or recurrent ischemic discomfort [2]. The use of nitroglycerin should not preclude the use of other drugs that have been shown to have more benefit, such as ACE inhibitors.

The drug of choice to manage the pain associated with STEMI is intravenous morphine sulfate [2]. Morphine sulphate is indicated to relieve ongoing ischemic discomfort, control hypertension, ameliorate anxiety, or manage pulmonary edema. The initial dose should be 4–8 mg, with lower doses in the elderly. Additional doses of 2–8 mg may be given at intervals of 5 to 15 minutes [2].

Beta Blockers

The use of beta blockers has been an established recommendation for patients with STEMI because of the drugs' association with lower mortality [2]. The recommendation was modified in the 2007 focused update of the ACC/AHA guideline because of safety issues related to the use of intravenous beta blockers in conjunction with fibrinolytic therapy as well as emerging data on a lack of survival benefit [259]. The findings were confirmed in the 2013 ACCF/AHA guideline, and it is still recommended that oral beta blockers be used within the first 24 hours, except for those subsets of patients at high risk for complications with use of beta blockers [2]. Beta blockers should not be used in patients with signs of heart failure, evidence of a low output state, increased risk of cardiogenic shock, or other relative contraindications to beta blockade.

ACE Inhibitors

The use of an oral ACE inhibitor is a strong recommendation for all patients recovering from STEMI, including those with anterior infarction, pulmonary congestion, or LVEF of less than 0.40, as well as those with normal LVEF in whom cardiovascular risk factors are well controlled [2]. Adherence to this recommendation has increased since the late 1990s but remains low [190; 261; 262; 263]. In addition, the doses used in clinical practice have been lower than the target doses used in clinical trials [263].

A meta-analysis of several major trials (more than 100,000 patients) demonstrated that use of an ACE inhibitor was associated with a significant overall odds reduction in mortality of 6.5% [264]. Early treatment is optimal, as reductions in mortality have been greatest within the first five days after the MI [264; 265]. The ACCF/AHA guideline for STEMI notes that it is preferable to initiate treatment with an ACE inhibitor within 24 hours [2]. Treatment should start at a low dose that is gradually increased to a full dose within 24 to 48 hours. ACE inhibitors are of most benefit for patients who are 55 to 74 years of age, have had an anterior infarct, or have a heart rate of at least 80 beats per minute [266]. Contraindications include a systolic blood pressure of less than 100 mm Hg (or more than 30 mm Hg below baseline), the presence of clinically relevant renal failure, a history of bilateral stenosis of the renal arteries, or known allergy. Patients who cannot tolerate an ACE inhibitor should be treated with an ARB [2].

Calcium-Channel Blockers

Early treatment with dihydropyridine calcium antagonists (nifedipine and nicardipine) has not been found to improve rates of mortality or reinfarction [2]. Nifedipine is contraindicated in the treatment of STEMI. Although verapamil and diltiazem may be useful to relieve ongoing or recurrent ischemia, lower blood pressure, or control the ventricular response rate to atrial fibrillation when beta blockers are contraindicated (and the patient has well-preserved left ventricular function and no clinical evidence of congestive heart failure or pulmonary congestion), no specific recommendation for their use exists in the 2013 STEMI guideline [2; 3]. Both drugs have been associated with significantly reduced mortality and major cardiovascular events [267; 268]. Verapamil should not be used for patients with heart failure or bradyarrhythmias, and diltiazem should not be used for patients with left ventricular dysfunction [2].

DISCHARGE PLANNING AND SECONDARY PREVENTION

Appropriate discharge planning and secondary prevention measures are essential, as the morbidity and mortality after UA/NSTEMI or STEMI are high (***Table 14***). A multidisciplinary team should be involved in preparing the patient for discharge, and detailed discharge instructions should be given to both the patient and family [2]. Discharge instructions should be easily understood, culturally sensitive, given in the patient's preferred language, and reinforced with written instructions. Instructions should include detailed information on the comprehensive care plan, including [2; 3]:

- Scheduling the first follow-up visit
- Returning to normal activities (e.g., driving, work, physical/sexual activities)
- Recommended secondary prevention measures
- Medication dosing, frequency, and adherence
- Plans to obtain prescribed medications immediately after discharge
- Referral to cardiac rehabilitation

OUTCOMES WITHIN FIVE YEARS AFTER FIRST MYOCARDIAL INFARCTION AMONG PATIENTS 45 YEARS OF AGE AND OLDER		
Outcome	**Prevalence**	
	Men	**Women**
Recurrent MI or fatal CHD	17%	21%
Heart failure	16%	22%
Stroke	4%	7%
MI = myocardial infarction; CHD = coronary heart disease.		
Source: [23]		*Table 14*

CARDIAC REHABILITATION

Exercise-based cardiac rehabilitation and secondary prevention programs have been shown to reduce repeat hospital admissions and improve health-related quality of life and function [269; 270]. Referral to a cardiac rehabilitation or secondary prevention program is a recommendation in the ACC/AHA guidelines for NSTE-ACS and STEMI [2; 3].

SECONDARY PREVENTION STRATEGIES

Substantial evidence has demonstrated that aggressive risk-reduction therapies enhance patient outcomes after ACS, and the 2014 AHA/ACC guideline for NSTE-ACS, the 2013 ACCF/AHA guideline for STEMI, and the 2011 update of the AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease guideline have made several recommendations for secondary prevention focusing on lifestyle modifications and medications.

Lifestyle Modifications

After an ACS event, patients should address modifiable risk factors associated with atherogenesis by changing certain behaviors. Lifestyle modifications will include improvements in diet and physical activity levels, smoking cessation, blood pressure control, lipid management, and diabetes management [2; 271]. Clinicians should involve other healthcare professionals in helping patients to achieve goals and should reinforce patients' positive efforts toward reaching these goals.

Smoking Cessation

What steps can healthcare professionals take to help improve adherence to smoking cessation?

Quitting smoking has been described as "probably the most important thing a smoker with acute MI can do to improve future health" [272]. Mortality after an ACS event for a patient who smokes cigarettes is twice that for a patient who does not, but cessation of smoking reduces reinfarction and death rates at one year [2]. Clinicians should use the in-hospital period after MI and each office visit as an opportunity to ask patients who were smokers if they have quit or are ready to quit and should offer counseling, pharmacologic support, and information on formal quit programs. The in-hospital period is unique because many patients are motivated to quit and are typically unable to smoke for three to nine days. Randomized controlled trials have shown that repeated contacts during the hospital stay and at and beyond three months (typically by telephone) are more likely to result in smoking cessation [2]. A Cochrane review showed that only intensive counseling programs work and that nicotine replacement further increases the rates of successful cessation among patients in intensive programs [273]. Another Cochrane review found high-quality evidence for a benefit of combined pharmacotherapy (with any type of nicotine-replacement therapy, bupropion, nortriptyline, or varenicline) and behavioral treatment compared with usual care, brief advice, or less intensive behavioral support [274]. However, many clinicians are reluctant to add another drug to the multitude of medications prescribed after MI.

Diet

What is the goal body mass index for patients after ACS?

Obesity is another well-documented risk factor for CHD, and weight management programs and information on healthy eating/caloric intake should be promoted as appropriate [271]. The patient's body mass index and waist circumference should be measured at each visit. The goal is to attain a body mass index of 18.5–24.9 and a waist circumference of 35 inches (women) or 40 inches (men) [271]. When weight reduction is needed, the initial goal is weight loss of 5% to 10% from baseline [271].

Exercise

The level of exercise should be prescribed according to risk, previous level of exercise, and possibly the results of a stress test [271]. The minimum goal is 30 minutes of aerobic exercise (e.g., walking, cycling, jogging) five times per week, with an optimal goal of 30 to 60 minutes every day [271]. Resistance training two times per week is reasonable to prescribe. Patients should also be encouraged to increase their routine daily activities (such as house cleaning and gardening).

Exercise-based secondary prevention programs are recommended for patients with STEMI and UA/NSTEMI.

(https://www.ahajournals.org/doi/10.1161/CIR.0b013e3182742c84. Last accessed January 10, 2022.)

Strength of Recommendation/Level of Evidence: IB (Procedure/treatment should be performed based on data derived from a single randomized clinical trial or nonrandomized studies evaluating limited populations.)

Medications

Four classes of medications are recommended after an ACS event: antiplatelet/anticoagulant agents (aspirin, warfarin, and a P2Y12 inhibitor), beta blockers, ACE inhibitors (or ARBs), and lipid-lowering agents [2; 3; 146; 271]. Treatment with these four classes has been associated with one-year mortality that is significantly lower than that for patients treated with none or one of the medications, with a positive impact most apparent at 24 months postdischarge, regardless of revascularization therapy [274; 275]. In addition, nitroglycerin should be prescribed for all patients, and they should be instructed on its use for ischemic pain [2]. The medication profile should be tailored to each patient on the basis of the in-hospital events and procedures, risk factors, and drug tolerability.

Antiplatelet/Anticoagulant Agents

The recommended antiplatelet therapy after discharge is a combination of aspirin and a P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor) [2; 146; 271]. The findings of studies have suggested that lower doses of aspirin (≤100 mg daily) are as effective as higher doses but have a better safety profile [180; 245; 248; 276]. The recommended daily dose of aspirin is 75–100 mg for all patients, and the ACC/AHA guidelines for the management of STEMI and NSTE-ACS and duration of dual antiplatelet therapy state that it is reasonable to use an 81-mg dose [2; 3; 146; 245; 248]. However, despite the better safety profile of low-dose aspirin, data have indicated that 325 mg is the most common dose, prescribed for 55.7% of patients with UA/NSTEMI [277].

The addition of clopidogrel to aspirin as maintenance therapy has been found to enhance outcomes for patients [245]. Among 12,562 patients with ACS who were taking aspirin (at a dose of 75–325 mg daily) in one trial, one year of treatment with clopidogrel was associated with a lower rate of a composite endpoint of cardiac death, MI, or stroke, regardless of the aspirin dose [245]. Clopidogrel was also associated with an increased risk for major bleeding, but bleeding risks increased with increasing aspirin dose, with or without clopidogrel [245].

The 2013 update of the ACCF/AHA guideline for the management of STEMI and the 2016 guideline focused update on duration of dual antiplatelet therapy include recommendations for maintenance therapy with a P2Y12 inhibitor [2; 248]. The guidelines indicate that patients with a stent should be treated with clopidogrel (75 mg daily), prasugrel (10 mg daily), or ticagrelor (90 mg twice a day) for at least one year [2; 248]. Patients not receiving a stent should receive clopidogrel (75 mg daily); it is reasonable to prescribe prasugrel (10 mg daily) in patients not receiving a stent and without a history of stroke or transient ischemic attack [2; 248].

Questions about clopidogrel maintenance therapy remain, as the optimal dose and duration of therapy have not been identified [146; 183; 278; 279]. Another concern is the effect of stopping clopidogrel. In a 2008 study of 3,137 patients with ACS (treated either medically or with PCI) who took clopidogrel for a mean of 9 to 10 months, there was a significantly high risk of adverse events in the initial 90 days after stopping treatment with clopidogrel [280]. The reason for this phenomenon is unclear, and the authors suggested that strategies to reduce the incidence of such early events should be identified [280]. Additionally, the response to clopidogrel varies among patients, and diminished responsiveness has been observed [146]. A 2010 retrospective study of 2,017 patients with ACS, conducted to confirm the findings of the 2008 study, found that the 0- to 90-day interval after stopping clopidogrel was associated with higher risk of death/MI compared with the 91- to 360-day interval. There was a similar trend of increased adverse events 0 to 90 days after stopping clopidogrel for various subgroups (i.e., women versus men, medical therapy versus PCI, stent type, and ≥6 months or <6 months of clopidogrel treatment) [281]. Warfarin is recommended as an antithrombotic for patients with UA/NSTEMI or STEMI who are allergic to aspirin [146; 271].

Antiplatelet therapy is preferred over anticoagulant therapy with warfarin (or other vitamin K agonists) for treating patients with atherosclerosis [271]. However, warfarin therapy is reasonable for patients with a prosthetic heart valve, persistent or paroxysmal atrial fibrillation, a documented left ventricular thrombus, concomitant venous thromboembolic disease, or other indication. Warfarin should be given to maintain a specific international normalized ratio (INR) depending on the use of stents, underlying cardiac disease, and the concomitant use of clopidogrel [271]. The risk of bleeding is increased when warfarin is used in conjunction with aspirin and/or clopidogrel, and patients treated with the three medications should be monitored closely [271].

Beta Blockers

Treatment with oral beta blockers is recommended for all patients after UA/NSTEMI or STEMI [2]. Treatment should continue indefinitely.

ACE Inhibitors or ARBs

An ACE inhibitor is also recommended as long-term therapy after UA/NSTEMI or STEMI [2; 271]. ARBs should be used for patients who are unable to tolerate an ACE inhibitor and have clinical or radiographic signs of heart failure or a left ventricular ejection fraction of less than 40% [2].

Lipid-Lowering Agents

Even before the advent of statins, reducing lipid levels through diet and previously available medications led to significant reductions in MIs. Statins are now the preferred medications for lipid-level management, and several studies have demonstrated their effectiveness in reducing atherogenesis. A fasting lipid profile should be determined within 24 hours after admission, and statin therapy should begin during hospitalization, regardless of this baseline level [2]. Intensive statin therapy appears to be of benefit for patients with recent ACS (but not for patients with stable CHD). In a pooled analysis of data on

more than 8,600 patients, intensive statin therapy significantly reduced all-cause mortality compared with standard therapy [282]. This benefit was confirmed in an analysis of data from a total of six trials (28,505 patients), with all-cause mortality at two years of 3.5% for intensive therapy compared with 4.6% for standard therapy [283]. A meta-analysis of 20 trials involving 8,750 patients with ACS undergoing PCI found a time-related benefit to the start of statin therapy. By meta-regression, earlier statin administration correlated significantly with lower risk of MI, major adverse cardiac events, and major adverse cardiac and cerebrovascular events [284].

The 2013 ACCF/AHA guideline for STEMI indicates the need to continue or initiate the use of a statin to manage patients' lipoprotein levels [2]. In particular, the guideline makes a sole recommendation for high-dose atorvastatin (80 mg daily), based primarily on results of the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial. Rates of cardiovascular events did not significantly decrease with tiered simvastatin (40 mg for one month, then 80 mg thereafter), and there are concerns about the safety of the 80-mg dose [2]. The compliance rate of statins may be improved when therapy is initiated before discharge following STEMI.

The goal of statin therapy is to achieve an LDL level less than 100 mg/dL for patients with average risk, and an LDL level of less than 70 mg/dL is reasonable for very-high-risk patients [2]. If the triglyceride level is 200 mg/dL or higher, the non-HDL cholesterol should be less than 130 mg/dL in patients with average risk, whereas a non-HDL cholesterol level of less than 100 mg/dL is reasonable for very-high-risk patients. Statin therapy should be supplemented with dietary modification, weight management, and exercise. Patients should be encouraged to follow a diet with an increase of fresh fruits and vegetables, with less than 7% of total calories as saturated fat, less than 1% of total calories as trans fatty acids, and less than 200 mg per day of cholesterol [2; 271].

If statin therapy fails to control lipid levels or patients do not tolerate statins, treatment with niacin or a bile acid sequestrant is reasonable [271]. Ezetimibe should be considered if patients do not tolerate any of the aforementioned medications [285].

Other Therapies

After discharge, patients may need other treatments to manage blood pressure, depression, or diabetes.

Control of Blood Pressure

In addition, blood pressure should be controlled according to the 2017 Guideline for High Blood Pressure in Adults, which recommends treatment when blood pressure is elevated, defined as 120–129/<80 mm Hg [67]. The guideline recommends initial treatment with nonpharmacologic interventions and lifestyle changes. Initiation of pharmacologic treatment is recommended for secondary prevention in patients with clinical cardiovascular disease and an average systolic blood pressure of 130 mm Hg or greater or an average diastolic blood pressure of 80 mm Hg or greater and for primary prevention in adults with an estimated 10-year atherosclerotic cardiovascular disease risk of 10% or higher and an average systolic blood pressure of 130 mm Hg or greater or an average diastolic blood pressure of 80 mm Hg or greater [67]. The AHA/ACCF recommends initial treatment with a beta blocker and/or an ACE inhibitor as secondary prevention for patients with CHD [271].

Treatment of Depression

An ACS event can be distressing for many patients, leading to a heightened fear of dying and anxiety about adjusting to life with cardiac disease [286]. These emotions can substantially affect a patient's psychosocial status and lead to depression [287; 288]. Some degree of clinically significant depression has been reported to occur in up to half of patients with ACS, with major depression occurring in 15% to 20% of patients [288]. Depression has been found more often in women compared with men and in men with a history of MI [289]. In addition to the negative effect on the patient's quality of life, depression has also been shown to be associated with lack of adherence to secondary prevention measures and with increased mortality [287; 290; 291].

Evaluation of a patient's psychosocial status, with particular attention paid to signs of depression, is a recommendation in the ACCF/AHA guidelines for STEMI and UA/NSTEMI, and screening for depression and referral and/or treatment is a recommendation in the 2011 AHA/ACCF Secondary Prevention and Risk Reduction Therapy guideline [2; 3; 271]. At each visit, clinicians should ask patients about anxiety, sleep disorders, social support, and symptoms of depression. Cognitive behavior therapy, sertraline, and selective serotonin reuptake inhibitors may be useful for enhancing the quality of life for patients with symptoms of depression, though treatment does not directly improve cardiovascular disease outcomes [271; 288].

Management of Diabetes

CHD is responsible for about 75% of deaths in individuals with diabetes, and more than 30% of patients with NSTE-ACS have diabetes [3]. It is now well known that a reduction in blood glucose levels is associated with improved outcomes in patients with diabetes or prediabetes who have experienced UA/NSTEMI or STEMI. This reduction may be achieved as the result of lifestyle changes (including weight management, physical activity, and medical nutrition therapy) or medication therapy [2; 3; 292]. The patient's primary care physician and/or endocrinologist typically handle the management of diabetes, but it is beneficial for treating physicians to coordinate with a primary care physician or specialist [271].

The goal of diabetes management (aside from reversal of the condition through intensive lifestyle change) is tight glycemic control, as both hyperglycemia and hypoglycemia have a profound impact on in-hospital and six-month mortality rates following a cardiac event [3]. Metformin is the recommended first-line diabetes pharmacotherapy for the prevention of cardiovascular complications [236]. The intensity of blood glucose-lowering medications should be closely tailored to each patient's risk of hypoglycemia during treatment. It may be reasonable to initiate treatment with medications to achieve an HbA1c of 7% or less [271].

Adherence and Compliance

Which issues negatively impact patients' adherence to medication therapy?

Despite the obvious benefit of secondary prevention strategies, physician adherence to guidelines and patient compliance with cardiac rehabilitation, medication regimens, and lifestyle change recommendations are suboptimal [271; 272; 293; 294; 295; 296; 297; 298]. According to data from several studies, referrals to cardiac rehabilitation range from 64% to 87% by hospital (mean: 81%) [295]. Quality improvement initiatives have increased referrals. Rates of actual enrollment are more important than referral rates, however, and enrollment has been much lower than referral rates [295; 296]. Only 29% of patients with MI who were referred to cardiac rehabilitation enrolled within one month of discharge; this rate raised to just 48.25% after six months [296]. Women are less likely to be enrolled after one month, as are patients with hypertension or peripheral arterial disease and uninsured patients. Older patients are less likely to have participated at six months, as are smokers and patients with economic hardship. White individuals and patients who attained a higher education level were more likely to enroll by six months [296].

Cardiac rehabilitation coordinators have identified several patient-related barriers to participation in rehabilitation programs as well as implementation of other evidence-based guidelines, including coming to terms with a diagnosis of heart disease, challenges in changing behavior, and cost [299]. Others have identified distance from a rehabilitation center (e.g., long travel time, lack of transportation) and high co-pays as significant barriers [296]. Efforts to improve rates of referral to cardiac rehabilitation should continue, and more research is needed to determine how to address barriers to enrollment.

Data have also indicated that rates of dietary change and smoking cessation in patients with ACS need improvement. Research shows that physicians are recommending dietary modification and smoking cessation to patients (91% and 95%, respectively), but rates of compliance are not optimal [272; 297; 300]. Smoking cessation rates following MI (roughly 30% at six months) are greater than in similar-age patients in the general population but are still too low [272].

Reasons provided for not adhering to dietary modification (and exercise) include not being able to see a physical change, and many individuals express that they are dissatisfied with having to make so many lifestyle changes at once [298]. However, the results of a 2014 study indicate that ACS patients who comply with nonsmoking, diet, and exercise plans have significantly lower mortality and recurrence of MI despite no change to their waist circumference [301]. Therefore, it is important that patients understand that the benefits of dietary modification are internal (not based on appearance) and that obtaining a regular lipid profile will show their progress.

With regard to medications, studies have shown that up to 57% of patients are not managed optimally, defined as receiving all four classes of medications [20; 104; 165; 188; 211; 261; 294; 300]. Optimal medical therapy is less likely among older patients, women, and patients who had CABG during the index hospitalization, had previous heart failure, or had renal dysfunction [275; 302; 303].

The class I guideline recommendations for all secondary prevention strategies can be organized into a simplified "ABCDE" approach to help clinicians implement guideline-based care [304]:

- A: Aspirin, antianginal agents, antiplatelet therapy, and ACE inhibitors (or ARBs)
- B: Beta blockers and blood pressure control
- C: Cardiac rehabilitation, cholesterol treatment, and cigarette smoking cessation
- D: Diet, depression management, and diabetes management
- E: Exercise and education

Critical pathways, protocols, and other quality improvement tools are valuable for helping to increase implementation of guidelines [20; 305]. For example, the GWTG program helps to enhance compliance through a Web-based tool that provides online reminders about discharge management strategies. This tool can be used to send discharge instructions and information on medications to primary care clinicians [20; 145]. The GWTG-Coronary Artery Disease program was implemented in 418 U.S. hospitals and was associated with widespread and prolonged adherence to evidence-based guidelines [305].

Lack of patient compliance with medications is also a serious problem and has been referred to as an unrecognized risk factor for CHD, because of its association with significant increases in adverse events and health costs [306; 307]. Among individuals with CHD (many of whom had experienced a recent ACS event), compliance with guideline-recommended medications has ranged from 18% to 55%. Approximately 54% of individuals have been compliant with all of their initial medications, and compliance decreases over time [307; 308; 309]. One study showed that compliance was 60.3% at one year, 53.7% at two years, and 48.8% at five years [310]. Individuals who

STRATEGIES FOR EFFECTIVE EDUCATION FOR ACS PATIENTS
Ask the patient what language he or she prefers for educational resources and use that language for oral education and written resources (as much as possible).
Assess the patient's baseline understanding of the disease and treatment.
Ask the patient what and how much he or she wants to know.
Discuss epidemiologic and clinical evidence.
Involve other healthcare specialists in the educational process.
Use a variety of educational resources in a variety of media.
Try innovative approaches, such as interactive modules.
Offer online resources to patients (e.g., the AHA website [https://www.heart.org] or the NHLBI website [https://www.nhlbi.nih.gov]).
Ascertain potential barriers to compliance.
Develop an action plan.
Have the patient focus on one behavior change at a time, if necessary. Involve family members in educational efforts.
Reinforce recommendations at all office visits.
Provide positive reinforcement for each step toward goals.
Provide telephone follow-up.
Source: [314; 315; 316; 317; 318] *Table 15*

discontinue medications are more likely to be older, female, unmarried, and less educated [309]. Several other factors have been found to be associated with noncompliance with medications [307; 308; 309]:

- Choice of medication
- Tolerability
- Duration of treatment
- Dosing frequency
- Higher number of prescribed medications
- Lack of symptoms as indication for the medication
- Uncertainty about how to take the medication
- Lack of transportation to the pharmacy

PATIENT EDUCATION

Patient education is an integral component of treatment for patients with ACS and should begin during hospitalization and continue throughout follow-up care [2]. Adequate time for appropriate education during the index hospitalization has been challenged by shorter hospital stays and reduced staffing [311]. The responsibility of patient education has thus shifted to the healthcare team. Surveys have shown that nearly one-half of individuals are not knowledgeable about ACS-related symptoms or their level of risk, even after having an ACS event [311]. Men, older individuals, and individuals with less formal education were less likely to be knowledgeable about their risk and symptoms [311]. This lack of knowledge can contribute to lack of compliance with recommended secondary prevention strategies.

Research has shown that patient education should focus on the importance of [2; 312]:

- Recognition of symptoms
- Timeliness of care
- Acknowledgment of risk factors for ACS
- Compliance with secondary prevention strategies

Education in these areas should be tailored to individuals, as perceptions of cardiac disease and risk differ across subgroups of patients according to age, gender, and race/ethnicity [137; 312]. As noted, many healthcare professionals do not feel confident in their effectiveness in helping patients understand their disease and comply with preventive measures [313]. ***Table 15*** provides a summary of strategies that nurses, physicians, and other healthcare team members can use to facilitate effective education with patients and families [314; 315; 316; 317; 318].

Recognition of Symptoms

Many individuals still believe that the onset of an MI will be "dramatic," with chest pain that is severe and crushing [2; 283; 319]. Among individuals who had an acute MI, 40% interpreted their symptoms as cardiac in nature [137]. In addition, chest pain and other ACS-related symptoms were interpreted differently by men and women. Men were more likely to think the symptoms were cardiac in nature if the chest pain was severe and if they had a history of CHD. In contrast, women did not relate severity of chest pain with a cardiac origin [137]. Healthcare professionals should talk to patients about the "real" signs and symptoms of ACS, emphasizing the diversity in symptoms [311; 312].

REASONS FOR DELAY IN SEEKING MEDICAL ATTENTION FOR CHEST PAIN
Expected more severe chest pain
Believed chest pain would resolve
Did not think symptoms were serious
Pain was localized in the back
Decided on "wait and see" approach
Thought symptoms were related to another condition (e.g., muscle strain, heartburn)
Was not aware of benefit of rapid action
Symptom onset occurred at home when individual was alone
Feared embarrassment if symptoms were not related to cardiac event
Underestimated personal risk of cardiac event
Source: [2; 283; 319; 320] *Table 16*

Timeliness of Care

On average, individuals wait 1.5 to 2 hours before seeking medical care for ACS-related symptoms, and this delay has not changed over time, despite many national public campaigns emphasizing the importance of timely care [2]. Furthermore, up to 50% of individuals with ACS-related symptoms are transported to the hospital by means other than emergency medical services, which can increase delays [2; 283]. Individuals have given several reasons for delays in seeking medical care (***Table 16***) [283]. Individuals and their families or caregivers should be told that immediate action is needed for ACS-related symptoms, including calling emergency medical services, taking nitroglycerin for ischemic pain, and taking aspirin.

Acknowledgement of Risk Factors

The need for better understanding of risk among individuals who have had ACS is evidenced by studies that have shown that perceptions of personal risk are lower than their actual risk [2; 283; 311; 312; 319]. Healthcare professionals should reinforce information about modifiable risk factors and provide patients with educational resources that describe risk factors and their effect on the potential for future events. Patients' individual risk factors should be discussed in an ongoing manner, with a focus on positive changes through lifestyle modifications and medications.

Compliance with Secondary Prevention Strategies

Compliance with prevention strategies can be enhanced by identifying the barriers for each individual patient and working together to address the problem. Primary care clinicians and other healthcare professionals should ask patients about medication compliance at each office visit and should emphasize the importance of maintaining drug therapy. Ongoing education about the benefit gained from medications as well as lifestyle modifications is vital to ensuring high compliance and low risk of adverse events.

ADHERENCE TO EVIDENCE-BASED GUIDELINES

Suboptimal adherence to guidelines for management and prevention of CHD contributes to increased ACS risk. Adherence has been less than effective, especially among patients at low risk for disease [2]. In one survey, primary care physicians, obstetricians/gynecologists, and cardiologists did not rate themselves as being effective in helping their patients to prevent CHD and manage risk factors. Of particular note is the percentage of respondents who were not aware that CHD leads to more deaths among women than among men; only 8% of primary care physicians, 13% of obstetricians/gynecologists, and 17% of cardiologists recognized this fact. Clinicians have noted several barriers to adhering to CHD prevention guidelines, including [2]:

- Cost of medications
- Lack of reimbursement, especially for lifestyle interventions
- Lack of adequate time for counseling
- Lack of patient education tools
- Existence of multiple guidelines
- Lack of knowledge and skills to recommend dietary changes and facilitate patient adherence

Efforts should be directed at alleviating these barriers to enable healthcare professionals to evaluate patients' risk factors adequately and to develop ways to help patients understand their risk and the importance of prevention strategies. A multidisciplinary team approach is needed to provide expertise in all areas. In addition, initiatives should emphasize the risk of CHD among women.

INTERPROFESSIONAL PRACTICE AND COLLABORATION

ACS represents the acute expression (recognition) of a chronic disease, one with pre-event possibilities for primary prevention and post-event need for secondary prevention and management strategies that restore and maintain health. Care of the patient with cardiovascular disease/ACS is challenging, the clinical issues multifaceted and complex for the patient, the patient's family, and the practitioner alike. Patients with chronic disease are estimated to visit four to nine different healthcare professionals regularly; interprofessional collaboration is an effective way to share the load, facilitate care, and reinforce management goals [321]. Evidence shows that an interprofessional team approach enhances quality of care and improves outcomes for patients with complex illness and diverse needs [322].

Interprofessional practice and collaboration (IPC) is a model of care provided by healthcare professionals with overlapping expertise, who are committed to shared responsibility, mutual trust, and communication to achieve a common goal [322]. Increasingly, IPC is modeled in the context of medical education. The introduction of IPC to primary care and chronic disease management has been shown to foster patient-centered care and reduce healthcare costs [323; 324].

SIMULATED CASE STUDIES

CASE STUDY 1

Patient E is a man, 54 years of age, who presented to his primary care physician's office with complaints of chest pain. Upon arrival at the primary care physician's office, he was chest pain free. A 12-lead ECG was performed and showed no changes from previous ECGs. The patient's vital signs were found to be stable and within his normal range: blood pressure 135/78 mm Hg, heart rate 68 beats per minute and regular, and respirations 16 breaths per minute and unlabored. He was afebrile.

***Comments and Rationale**: Persons who present in any healthcare setting with a complaint of chest pain should be evaluated for the presence of signs and symptoms of ACS. Appropriate assessment measures include vital signs and a 12-lead ECG to assess for changes suspicious for ischemia or infarct. Patient E was chest pain free on arrival, his ECG did not show any acute ischemic changes, and his vital signs were stable. Further assessment by the healthcare provider is indicated.*

The physician questioned Patient E about his chest pain episodes. The patient reported that, until about a week ago, he just had been having his "usual" occasional chest pain when he "worked too long, too hard in the yard." However, over the last week, his chest pain attacks had been lasting longer and requiring more sublingual nitroglycerin tablets for relief. The previous night he had experienced a prolonged episode of chest pain at rest and decided to seek medical attention.

***Comments and Rationale**: Chest pain that occurs in a predictable pattern, is generally triggered by the same level of exertion, and is readily relieved by rest and sublingual nitroglycerin can be classified as "stable angina." Stable angina is a hallmark symptom of CHD but is rarely indicative of acute myocardial ischemia. However, chest pain attacks that increase in frequency, severity, and/or require additional nitroglycerin tablets to achieve relief and severe chest pain that occurs at rest are indications that the patient's angina has become "unstable." Immediate medication evaluation and intervention is indicated.*

The physician reviewed Patient E's medical record and noted that he had a history of CABG surgery five years previously. Two years ago, Patient E required placement of a drug-eluting stent to open a blockage in one of the saphenous vein grafts from his prior CABG surgery. Patient E was also prescribed medication for dyslipidemia; his most recent laboratory tests showed his LDL was borderline high at 135 mg/dL. He stopped smoking following the stent placement two years previously. The patient was approximately 30 pounds overweight. When the physician mentioned his need for weight loss, the patient's usual reply was, "It's either the weight or the smoking. I can't manage both."

***Comments and Rationale**: A careful history and physical can provide information necessary to triage patients who present with chest pain and stratify their risk for serious consequences such as acute MI. Major risk factors for ACS include a known history of CHD, history of occlusions that have required intervention to restore blood flow and oxygen supply, and the presence of modifiable risk factors such as obesity, dyslipidemia, smoking, and hypertension.*

Given the patient's known CHD, previous history of CABG and PCI with stents, and his continuing risk factors, the physician instructed Patient E to go to the emergency department of the local hospital. The patient declined transport by emergency medical services and insisted on driving himself to the hospital.

***Comments and Rationale**: ACCF/AHA guidelines strongly recommend that persons with possible ACS be transported to the hospital by emergency medical services. Transport by emergency medical services provides the opportunity for skilled healthcare providers to assess the patient, obtain an immediate ECG, and administer aspirin and other therapies as indicated. In addition, emergency medical services can notify the receiving emergency department to expect the patient so immediate triage and evaluation are facilitated. ACCF/AHA guidelines strongly discourage persons with possible ACS from driving themselves or asking friends or family members for transport to the emergency department.*

In the emergency department, Patient E developed an episode of chest pain. He rated the pain as 10 out of 10 and located the pain on the left side of his chest, substernal region. He was slightly diaphoretic with a blood pressure of 170/90 mm Hg and a heart rate of 110 beats per minute.

***Comments and Rationale**: Severe, intense chest pain located in the left substernal area of the chest coupled with diaphoresis and vital sign changes is a strong indicator of ACS.*

The emergency physician activated the chest pain protocol. Patient E received 325 mg of aspirin with instructions to chew it before swallowing. He was also given sublingual nitroglycerin, and supplemental oxygen at 2 liters per nasal cannula was started. A 12-lead ECG was performed, and blood work, including troponin T level, were drawn.

***Comments and Rationale**: In ACS, aspirin is given immediately for its antiplatelet action to decrease the risk of thrombus formation. Sublingual nitroglycerin acts a vasodilator, reducing myocardial workload while increasing myocardial oxygen supply. It also helps to lower elevated blood pressure.*

The 12-lead ECG showed non-specific ST-segment and T-wave changes. Five minutes after one sublingual nitroglycerin tablet, the patient reported that his chest pain was 10/10; his blood pressure was 140/88 mm Hg. A second sublingual nitroglycerin tablet was given; five minutes later, Patient E reported his pain was 8/10, and his blood pressure remained at about 140/88 mm Hg. A third sublingual nitroglycerin tablet was administered, and minutes later, the patient reported that his pain was 5/10. His blood pressure was measured as 132/80 mm Hg. The physician ordered 2 mg of morphine IV.

***Comments and Rationale**: In patients with clinical symptoms of ACS, nonspecific ST-segment and T-wave changes are worrisome. Serial ECGs may be indicated to identify the presence of an evolving MI. Sublingual nitroglycerin may be given every five minutes up to three doses if the patient does not become hypotensive. The goal of analgesic therapy in ACS is to get the patient "chest pain free." Morphine may be used to treat chest pain that does not resolve after three sublingual nitroglycerin tablets. Morphine acts as a vasodilator, decreasing myocardial oxygen demands and increasing myocardial oxygen supply.*

After receiving morphine, Patient E reported that he was chest pain free. His blood pressure and heart rate returned to the "usual" level. His initial troponins were returned negative for cardiac damage. The physician made the decision to admit the patient to the telemetry/stepdown floor for further observation and monitoring. His admitting diagnosis was UA/possible ACS, and his admitting orders included orders for serial troponin monitoring, continuous ECG monitoring, and immediate 12-lead ECG with chest pain.

***Comments and Rationale**: The combination of Patient E's increasingly severe and frequent chest pain episodes coupled with the presence of nonspecific changes on 12-lead ECG and his previous history of CHD, CABG, and stent placements are indicators that the patient is at increased risk for MI. Serial troponins can provide important diagnostic information and may be used to confirm or rule out a diagnosis of NSTEMI. Continuous ECG monitoring provides information about ST-segment changes indicative of ischemia and infarct. A 12-lead ECG recorded during chest pain can also provide information about possible ischemia/infarction and what part of the heart is at risk.*

Patient E's second set of cardiac biomarkers returned showing elevated troponin levels. A repeat ECG indicated no evidence of ischemia or infarct. A third set of cardiac biomarkers approximately eight hours later showed that troponin T was positive for myocardial damage. A diagnosis of NSTEMI was confirmed. Another ECG taken immediately after the return of the laboratory work did not show any evidence of ischemia; however, minutes later, Patient E developed chest pain. ST-segment depression in the inferior leads was noted on continuous ECG monitoring.

***Comments and Rationale**: ECG changes and cardiac biomarker elevation indicative of myocardial ischemia and infarction can develop over a period of minutes to hours. In persons who have persistent chest pain with initial negative ECG findings and cardiac biomarker levels, serial measurements are indicated. As was the case with Patient E, biomarker changes indicative of infarct may develop several hours after the initial episode of chest pain. Presence of elevated cardiac troponin levels, in the absence of ST-segment elevation, is diagnostic for NSTEMI.*

The physician ordered a continuous heparin infusion along with a bolus dose of eptifibatide followed by a continuous infusion. Patient E had been administered aspirin in the emergency department; on the floor, he received 600 mg of clopidogrel along with a low dose of a beta blocker. Patient E developed another episode of chest pain that was not relieved by sublingual nitroglycerin or IV morphine. As a result, the physician ordered a continuous nitroglycerin drip.

***Comments and Rationale**: The immediate goal of treatment in NSTEMI is to relieve ischemia and prevent ongoing infarction. Key elements of management include aspirin (chewed) and clopidogrel to reduce platelet formation and aggregation, and nitroglycerin and morphine for relief of ischemic pain through reduction of myocardial workload and decrease in myocardial oxygen demand. Chest pain unrelieved by sublingual nitroglycerin may be treated with a continuous nitroglycerin infusion titrated to relieve chest pain and maintain a blood pressure within a prescribed range. A third major element in the management of acute NSTEMI is anticoagulation. A continuous heparin infusion is one option for anticoagulation; use of heparin may be combined with the use of a glycoprotein IIb/IIIa inhibitor. In acute stages of NSTEMI, a glycoprotein IIb/IIIa inhibitor such as eptifibatide may be used. Eptifibatide may be initiated prior to cardiac catheterization, and the infusion can be maintained for a specified period of time following catheterization and stent placement.*

Patient E was taken to the cardiac catheterization laboratory for diagnostic coronary angiography and possible PCI. Cardiac catheterization revealed that he had an area of blockage in his right coronary artery. The patient's previous stent remained open, and the other vein grafts from previous surgery were also patent. A PCI with placement of a bare-metal stent was performed.

***Comments and Rationale**: Intracoronary stents are deployed during PCI to help to keep the lumen of the affected vessel open. The choice of type of stent (bare-metal or drug-eluting) is left to the interventional cardiologist performing the procedure.*

Following recovery in the cardiac catheterization area, Patient E was returned to his room. The postcatheterization orders included instructions for bed rest for 4 hours, continuation of the eptifibatide drip for a total of 18 hours following the conclusion of the PCI procedure, and serial monitoring of cardiac biomarkers and complete blood count. Nursing care included continuous ECG monitoring, frequent vital sign checks, frequent monitoring of the arterial puncture site for evidence of bleeding or hematoma, and assessment for signs of recurrent chest pain (indicative of reocclusion of the infarct-related vessel) or severe left flank pain (indicative of retroperitoneal bleed). Patient E was encouraged to drink fluids, and his urine output was monitored and recorded.

***Comments and Rationale**: Key elements of care during the immediate post-PCI period include monitoring for bleeding, maintaining the eptifibatide drip as ordered to decrease the risk of stent occlusion, and monitoring the patient for changes in vital signs, heart rhythm, or the development of chest pain. Potential complications during this period include bleeding from the puncture site and reocclusion in the coronary artery.*

Patient E's initial blood work following the PCI showed a drop in his platelet count from the high normal to borderline low range. A second set of blood work sent six hours later showed a dramatic and significant drop in his platelet count. The physician was notified and ordered the discontinuation of the eptifibatide infusion. Appropriate nursing interventions included close monitoring of the patient for any signs of bleeding.

***Comments and Rationale**: Use of glycoprotein IIb/IIIa inhibitors can cause an unsafe drop in platelet counts in some individuals. Careful monitoring of platelet levels at specified intervals during the infusion is indicated to identify this complication promptly and intervene in timely fashion.*

CASE STUDY 2

Patient Z, a woman 63 years of age, presented to the emergency department with a complaint of intermittent epigastric and chest discomfort. She reported that the discomfort had occurred intermittently over the previous two to three weeks. When questioned, she admitted that she had felt more fatigued and had periods of shortness of breath and light-headedness over the same time period.

***Comments and Rationale**: While women may present with ACS symptoms similar to men, they may also present with symptoms labeled as "atypical." Epigastric pain, fatigue, and light-headedness have been identified as "atypical" symptoms associated with ACS.*

At the time of presentation to the emergency department, Patient Z reported that she was experiencing no discomfort. Her blood pressure was elevated at 210/120 mm Hg, her heart rate was 84 beats per minute, her respirations were even and easy, and she did not appear to be in acute distress. An initial ECG showed no signs of acute ischemia or infarct but did reveal a pathologic Q wave. The initial cardiac troponin I returned indicating the level to be "borderline" but not yet elevated. When asked, Patient Z admitted that she has had high blood pressure "for a while" and that she does not always take her medications as prescribed.

***Comments and Rationale**: At the time of admission to the emergency department, Patient Z shows no signs of acute ischemia or infarct; she is chest pain free, her ECG shows no ST-segment elevation or ST-segment depression, and her initial cardiac troponin level is equivocal. However, she has at least one major risk factor for CHD and subsequent ACS: hypertension that appears poorly controlled. Her ECG also shows evidence (i.e., a pathologic Q wave with no evidence of ST-segment elevation or T-wave inversion) that she had experienced an MI sometime in the past.*

The emergency department physician admitted Patient Z to the telemetry unit with hypertension and possible ACS/UA. Serial cardiac biomarkers remained essentially unchanged from the initial levels. Repeat 12-lead ECG eight hours after admission showed no indications of acute ischemia or infarct. Patient Z had several episodes of epigastric discomfort/chest discomfort following her transfer to the telemetry unit. She developed nausea and emesis with one episode. Sublingual nitroglycerin was effective in relieving her discomfort. Oral medications to lower her blood pressure were effective and subsequent measurements indicated a blood pressure of 150/88 mm Hg. When asked, the patient denied any history of a previous MI. When asked if a physician had ever instructed her to take a lipid-lowering medication, she replied that she "couldn't afford it."

***Comments and Rationale**: Risk stratification indicates that Patient Z has risk factors for CHD and ACS but is not currently experiencing an acute episode. An early conservative approach, including a stress test, is indicated.*

The physician ordered a fasting lipid panel, to evaluate for dyslipidemia, and an exercise stress test.

***Comments and Rationale**: The focus of medical therapy for Patient Z will be on continued risk stratification and risk factor reduction. Exercise stress testing will provide information about presence of ischemic disease and risk for adverse cardiac events.*

During the exercise stress test, Patient Z developed chest pain, diaphoresis, and nausea before reaching the targeted heart rate. She underwent a follow-up cardiac catheterization with placement of a stent in her right coronary artery. Following a conversation with the patient regarding adherence to dual antiplatelet therapy, the interventional cardiologist chose to implant a bare-metal stent.

***Comments and Rationale**: Inability to reach a heart rate target due to development of chest pain or other ischemia-associated symptoms during a stress test is an indication of ischemic disease and high risk for future ischemia and infarct. Cardiac catheterization is indicated; it provides direct visualization of coronary circulation and permits percutaneous intervention if indicated. Implantation of drug-eluting stents should generally be avoided in persons for whom adherence to dual antiplatelet therapy is unlikely.*

Patient Z recovered uneventfully from the PCI. Her prescribed medications included simvastatin, metoprolol, hydrochlorothiazide, additional oral antihypertensive medications, her "usual" oral hypoglycemic medications, aspirin, and clopidogrel. Patient Z's fasting lipid panel showed an LDL level of 190 mg/dL and a total cholesterol of 250 mg/dL. The discharge nurse began planning for Patient Z's return home.

***Comments and Rationale**: Unless complications develop, patients only remain in the hospital 24 to 48 hours after PCI. Therefore, assessment of discharge needs and initial teaching should begin immediately.*

The nurses caring for Patient Z noted that she was taking several medications that were new to her: simvastatin, metoprolol, aspirin, and clopidogrel. From the admission assessment, the nurse saw that the patient stopped taking her previously prescribed statin because of its cost. She also noted that Patient Z's fasting lipid levels were high; some diet teaching might be helpful in assisting the patient to modify her diet and reduce this risk factor. The nurse referred Patient Z to social work for possible financial assistance with medications and to the dietician for assistance with diet changes. When questioned, the patient stated that she preferred written information in English, so written material on reducing cholesterol and triglyceride consumption were provided as well as a list of local resources. The nurse also reviewed all of Patient Z's current medications with her when she administered them, stressing the importance of taking them as prescribed and making sure that the patient understood the purpose and prescribed dosage of all her new medications. Provided education and the patient's responses were recorded in the patient's medical record.

***Comments and Rationale**: Patient education should be provided in the language and format that the patient prefers. Teaching about new medications and facilitating the patient's ability to obtain medications after discharge through referral to social work or appropriate resources is very important. Short hospital stays do not permit time for exhaustive, extensive education. Written materials and referrals that the patient can use to follow up on recommended lifestyle changes are therefore helpful. Risk reduction for Patient Z will involve major lifestyle changes. Healthcare practitioners in all settings who encounter this patient will have a role to play in promoting increased adherence to recommended measures.*

CONCLUSION

The identification of the pathophysiologic process leading to ACS has redefined the treatment of this spectrum of cardiac disorders, and researchers continue to refine therapeutic options to produce optimal patient outcomes. Despite a shared initiating event (plaque rupture or erosion), UA/NSTEMI and STEMI are distinct clinical entities, with differences in pathophysiology, clinical presentation, treatment, and prognosis. The diagnosis of UA/NSTEMI (also known as NSTE-ACS) relies primarily on elevated levels of cardiac troponins and the lack of ST-segment elevation on ECG. By contrast, the diagnosis of STEMI is made solely on ECG findings. After the type of MI has been determined, complex decision making is required to determine the appropriate course of treatment.

The goal of immediate treatment of NSTE-ACS is relief of ischemia and prevention of recurrent ischemic events. Risk stratification is essential for determining whether an early invasive or ischemia-guided strategy is best for the patient. Antiplatelet therapy, P2Y12 inhibitors, and antithrombotic therapy are adjuncts to treatment. With STEMI, the goal of immediate treatment is re-establishment of blood flow to the heart. The crucial factor for determining the treatment approach is timing from the onset of symptoms to treatment and from arrival in the emergency department to treatment. The preferred option for reperfusion is PCI, but the recommended 90-minute door-to-balloon time is difficult to achieve in most cases. However, there is an increased emphasis on developing systems of care that increase patient access to primary PCI. The other option for reperfusion, fibrinolytic therapy, has the advantage of immediately re-establishing blood flow, but it is associated with lower rates of reperfusion and higher risks compared with PCI. Ancillary therapy with antiplatelet therapy, P2Y12 inhibitors, and antithrombotic therapy is used to maintain patency of the infarct-related artery and prevent reocclusion.

Review of data from several large-scale studies, cardiac registries, and quality improvement initiatives has shown that adherence to guideline recommendations for the diagnosis, treatment, and secondary prevention NSTE-ACS and STEMI are suboptimal, particularly for older individuals, women, and minority populations. In addition, an inverse relationship has been found between risk and treatment, with more low-risk patients than high-risk patients receiving aggressive treatment. The data have also demonstrated a clear benefit in survival and outcomes when guideline recommendations are followed. Thus, clinicians should become more familiar with these guidelines and should encourage hospitals to implement system-wide policies and procedures to facilitate guideline-driven care. The use of protocols, clinical pathways, and standardized order forms can help to ensure that all patients receive appropriate care in a timely manner. After discharge, effective communication among the treating physician, the healthcare team, the patient and family, and the patient's primary care clinician is essential for ensuring long-term compliance with lifestyle modifications and medications, which will help to reduce the risk of future cardiac events.

RESOURCES

American Heart Association
1-800-242-8721
https://www.heart.org

American Cancer Society
1-800-227-2345
https://www.cancer.org

American Lung Association
1-800-586-4872
https://www.lung.org

DASH Diet Eating Plan
https://dashdiet.org

D2B Sustain the Gain
https://www.d2balliance.org

Assessing Cardiovascular Risk: Systematic Evidence Review from the Risk Assessment Work Group
https://www.nhlbi.nih.gov/health-topics/assessing-cardiovascular-risk

Global Registry of Acute Coronary Events (GRACE)
https://www.outcomes-umassmed.org/grace

National Heart, Lung, and Blood Institute
1-877-645-2448
https://www.nhlbi.nih.gov

TIMI Study Group
1-800-385-4444
http://www.timi.org

Customer Information/Evaluation insert located between pages 52–53.

Course Availability List

These courses may be ordered by mail on the Customer Information form located between pages 52–53.
We encourage you to **GO GREEN**. Access your courses **online** or download as an **eBook** to save paper and **receive a discount** or sign up for **One Year of Unlimited Online APRN CE starting at only $125!** Additional titles are also available.

www.NetCE.com

Like us at NetCE4Nurses

MODERATE SEDATION/ANALGESIA

#30464 • 15 ANCC / 15 Pharm Hours

Book By Mail – $98 • ONLINE – $90

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, outpatient surgery, intensive care, and emergency departments.
Additional Approval: AACN Synergy CERP Category A, CCMC

POSTOPERATIVE COMPLICATIONS

UPDATE

#30763 • 15 ANCC / 1 Pharm Hour

Book By Mail – $98 • ONLINE – $90

Purpose: The purpose of this course is to provide nurses and all allied health professionals who care for postsurgical patients the knowledge necessary to recognize and manage common postoperative complications, improving patient care and outcomes.
Faculty: Susan Engman Lazear, RN, MN
Audience: This course is designed for all nurses and allied professionals involved in the care of patients who undergo surgical procedures, especially those who work in the preoperative area, the operating room, or the postanesthesia unit in hospitals or free-standing surgical centers.
Additional Approval: AACN Synergy CERP Category A, CCMC

RURAL PUBLIC HEALTH AND NURSING CARE

#31961 • 15 ANCC Hours

Book By Mail – $98 • ONLINE – $90

Purpose: The purpose of this course is to provide nurses with the knowledge and skills necessary to provide optimum care to rural residents and to advocate for the needs of this population.
Faculty: Mary Schmeida, RN, PhD
Audience: This course is designed for nurses in all practice settings with patients from rural communities.
Additional Approval: AACN Synergy CERP Category C, CCMC

MULTIMODAL PHARMACOTHERAPY FOR PAIN MANAGEMENT

NEW! Pain Mgmt

#35270 • 5 ANCC / 5 Pharm Hours

Book By Mail – $38 • ONLINE – $30

Purpose: The purpose of this course is to provide healthcare providers with a clear understanding of the concept of multimodal pharmacotherapy for pain relief, including available classes of analgesics.
Faculty: Richard E. Haas, BSN, MSN, EdM, PhD, CRNA, PHRN
Audience: This course is designed for nurses involved in the care of patients with pain.
Additional Approval: AACN Synergy CERP Category A
Special Approval: This course is designed to meet the requirements for pain management education .

HIPAA PRIVACY AND SECURITY

NEW!

#91140 • 5 ANCC Hours

Book By Mail – $38 • ONLINE – $30

Purpose: The purpose of this course is to provide information that will allow health and mental health professionals to more easily comply with the Privacy and Security Rules defined by HIPAA.
Faculty: Carol Shenold, RN, ICP
Audience: This course is designed for all members of the interprofessional healthcare team.
Additional Approval: AACN Synergy CERP Category B

CLINICAL CARE OF THE TRANSGENDER PATIENT

#91922 • 10 ANCC / 5 Pharm Hours

Book By Mail – $68 • ONLINE – $60

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, and nurses, involved in the care of transgender patients.
Additional Approval: AACN Synergy CERP Category A, CCMC

Are you licensed in other states?
Our Unlimited Online Special Offer includes all state mandates!
www.NetCE.com/APRNUnlimited

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

Course Availability List *(Cont'd)*

HYPERTENSION: STRATEGIES TO IMPROVE OUTCOMES

UPDATE

#94223 • 5 ANCC / 5 Pharm Hours

Book By Mail – $38 • ONLINE – $30

Purpose: The purpose of this course is to provide healthcare professionals with the information necessary to develop treatment regimens associated with optimal adherence and provide adequate patient education, counseling, and support to patients with hypertension.
Faculty: John J. Whyte, MD, MPH
Audience: This course is designed for all physicians, physician assistants, nurses, and pharmacy professionals involved in the care of patients with hypertension.
Additional Approval: AACN Synergy CERP Category A, CCMC

OSTEOARTHRITIS

New Guidelines

#94954 • 10 ANCC / 5 Pharm Hours

Book By Mail – $68 • ONLINE – $60

Purpose: The purpose of this course is to provide healthcare professionals with the information necessary to adequately assess osteoarthritis symptoms, treat osteoarthritis patients based on evidence-based guidelines, and appropriately refer to specialists.
Faculty: Lori L. Alexander, MTPW, ELS, MWC
Audience: This course is designed for physicians, physician assistants, nurses, and other healthcare professionals involved in the care of patients with osteoarthritis.
Additional Approval: AACN Synergy CERP Category A, CCMC

PSYCHOPHARMACOLOGY

#95230 • 10 ANCC / 10 Pharm Hours

Book By Mail – $68 • ONLINE – $60

Purpose: The purpose of this course is to provide members of the interprofessional healthcare team with the information necessary to appropriately prescribe, administer, and dispense psychopharmacotherapy, with the ultimate goal of improving patient care and public health.
Faculty: Carol Whelan, APRN
Audience: This course is designed for nurses and pharmacy professionals involved in the care of patients with mental health conditions.
Additional Approval: AACN Synergy CERP Category A

ATTENTION DEFICIT HYPERACTIVITY DISORDER

#96213 • 5 ANCC / 2 Pharm Hours

Book By Mail – $38 • ONLINE – $30

Purpose: Attention deficit hyperactivity disorder (ADHD) has a significant effect on day-to-day functioning and quality of life; however, it often goes unrecognized. The purpose of this course is to educate healthcare professionals about the epidemiology, diagnosis, and management of ADHD.
Faculty: John J. Whyte, MD, MPH; Paul Ballas, DO
Audience: This course is designed for all physicians, nurses, and social work/counseling groups involved in the care of patients with attention deficit hyperactivity disorder.
Additional Approval: AACN Synergy CERP Category A, CCMC

DEPRESSION AND SUICIDE

UPDATE

#96404 • 15 ANCC / 2 Pharm Hours

Book By Mail – $98 • ONLINE – $90

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

ANXIETY DISORDERS IN OLDER ADULTS

NEW!

#96690 • 3 ANCC / 1 Pharm Hour

Book By Mail – $26 • ONLINE – $18

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

CANNABIS AND CANNABIS USE DISORDERS

#96973 • 5 ANCC / 5 Pharm Hours

Book By Mail – $38 • ONLINE – $30

Purpose: The purpose of this course is to allow healthcare professionals to effectively identify, diagnose, treat, and provide appropriate referrals for patients with cannabis use disorders.
Faculty: Mark Rose, BS, MA, LP
Audience: This course is designed for health and mental health professionals who are involved in the evaluation or treatment of persons who use cannabis, either illicitly or as an adjunct to medical treatment.
Additional Approval: AACN Synergy CERP Category A

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

Course Availability List *(Cont'd)*

PALLIATIVE CARE AND PAIN MANAGEMENT AT THE END OF LIFE

#97383 • 15 ANCC / 10 Pharm Hours

Book By Mail – $98 • ONLINE – $90

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

Faculty: Lori L. Alexander, MTPW, ELS, MWC

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

Additional Approval: AACN Synergy CERP Category A, CCMC

CHILD ABUSE IDENTIFICATION AND REPORTING: THE NEW YORK REQUIREMENT

NY Mandate

#97533 • 2 ANCC Hours

Book By Mail – $23 • ONLINE – $15

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, and other professionals 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.

COMMONLY ABUSED SUPPLEMENTS

NEW!

#98020 • 2 ANCC Hours

Book By Mail – $23 • ONLINE – $15

Purpose: The purpose of this course is to provide healthcare professionals in all practice settings the knowledge necessary to increase their understanding of the commonly abused supplements and their adverse effects.

Faculty: Chelsey McIntyre, PharmD

Audience: This course is designed for healthcare professionals whose patients are taking or are interested in taking dietary supplements.

Additional Approval: AACN Synergy CERP Category A

GETTING TO THE POINT: ACUPUNCTURE AND ACUPOINT THERAPIES

NEW!

#98030 • 4 ANCC Hours

Book By Mail – $32 • ONLINE – $24

Purpose: The purpose of this course is to provide healthcare professionals in all practice settings the knowledge necessary to increase their understanding of acupoint and acupressure therapies.

Faculty: Chelsey McIntyre, PharmD

Audience: This course is designed for healthcare professionals whose patients are using or are interested in using acupoint and acupressure therapies.

Additional Approval: AACN Synergy CERP Category A

DIZZINESS AND VERTIGO

#98401 • 10 ANCC / 5 Pharm Hours

Book By Mail – $68 • ONLINE – $60

Purpose: The purpose of this course is to provide clinicians with the information necessary to appropriately diagnose and treat causes of dizziness and vertigo and improve patients' quality of life.

Faculty: Mark Rose, BS, MA, LP

Audience: This course is designed for physicians and nurses involved in the diagnosis, treatment, and care of patients with dizziness and/or vertigo.

Additional Approval: AACN Synergy CERP Category A, CCMC

INFECTION CONTROL: THE NEW YORK REQUIREMENT

NY Mandate

#98643 • 5 ANCC / 1 Pharm Hour

Book By Mail – $38 • ONLINE – $30

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, MWC; Carol Shenold, RN, ICP

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 A

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 #OT10781.

PARKINSON DISEASE

UPDATE

#98772 • 10 ANCC / 5 Pharm Hours

Book By Mail – $68 • ONLINE – $60

Purpose: The purpose of this course is to provide physicians, nurses, and other members of the interprofessional healthcare team a review of pathogenesis, disease progression, diagnosis, and management of Parkinson disease, in order to improve patient care and quality of life.

Faculty: Mark Rose, BS, MA, LP

Audience: This course is designed for all healthcare providers in the primary care setting who may encounter patients with Parkinson disease.

Additional Approval: AACN Synergy CERP Category A, CCMC

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

NetCE
a trchealthcare brand

Customer Information

(Incomplete information may delay processing.)

For office use only:
APRN23

Please print your Customer ID # located on the back of this catalog. (Optional)

Order/complete by mail
P.O. Box 997571
Sacramento, CA 95899-7571
Order/complete by fax
(916) 783-6067
Contact us
(800) 232-4238
Email us
help@NetCE.com

Order/complete online
www.NetCE.com/APRN23

Last Name First Name MI

State License # Exp.

State Additional License # Exp.

License Type (circle one): APRN / APN / ARNP / CNP / CRNP / CNS / CRNA / CNM / LM / NP / Other:

Address

City State Zip

Phone ( )

Fax ( )

Email

☐ Sign me up for NetCE Alerts, Promotions, License Reminders, and More!

Receive certificate(s) by:
- ☐ Online Access - FREE! Email required
- ☐ Email - FREE!
- ☐ Fax - FREE!
- ☐ Mail - Add $6 for shipping and handling

Complete before January 31, 2024, pay
$62

Complete after January 31, 2024, pay
$73

ENCLOSED SPECIAL OFFER: 30 HOURS

(23 Pharmacology Hours)

You may complete ALL three of these courses for a maximum payment of $62 (or pay the individual course price).

✓	Course #	Course Title / Contact Hours	Price
☐	95500	Opioid Safety: Balancing Benefits and Risks / 5 Contact Hours	$30
☐	96790	Psychedelic Medicine and Interventional Psychiatry / 10 Contact Hours	$60
☐	30993	Acute Coronary Syndrome / 15 Contact Hours	$90

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

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

✓	Course #	Course Title / Contact Hours	Price	✓	Course #	Course Title / Contact Hours	Price
☐	30464	Moderate Sedation/Analgesia / 15	$98	☐	96404	Depression and Suicide / 15	$98
☐	30763	Postoperative Complications / 15	$98	☐	96690	Anxiety Disorders in Older Adults / 3	$26
☐	31961	Rural Public Health and Nursing Care / 15	$98	☐	96973	Cannabis and Cannabis Use Disorders / 5	$38
☐	35270	Multimodal Pharmacotherapy for Pain Mgmt / 5	$38	☐	97383	Palliative Care and Pain Management at the EOL / 15	$98
☐	91140	HIPAA Privacy and Security / 5	$38	☐	97533	NY Child Abuse Identification and Reporting / 2	$23
☐	91922	Clinical Care of the Transgender Patient / 10	$68	☐	98020	Commonly Abused Supplements / 2	$23
☐	94223	Hypertension: Strategies to Improve Outcomes / 5	$38	☐	98030	Getting to the Point: Acupuncture & Acupoint Therapies / 4	$32
☐	94954	Osteoarthritis / 10	$68	☐	98401	Dizziness and Vertigo / 10	$68
☐	95230	Psychopharmacology / 10	$68	☐	98643	NY Infection Control / 5	$38
☐	96213	Attention Deficit Hyperactivity Disorder / 5	$38	☐	98772	Parkinson Disease / 10	$68

☐ Check or Money Order (*payable to NetCE*)
☐ VISA / MasterCard / AmEx / Discover

Please print name (as shown on credit card)

Credit card #

/

Expiration date Security code

Security code is last three numbers in the signature area on back of credit card or four numbers above the account number on front of AmEx cards.

Signature

Special Offer (before January 31, 2024) $62
$73 (after January 31, 2024)
I would like my certificates mailed for an additional $6
Additional Courses
Subtotal
Expedited Delivery
Grand Total

Expedited mail delivery within 2 to 3 days is available in most areas at an additional charge of $35. Call for information on international delivery.

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

NetCE
a trchealthcare brand

Evaluation
(Completion of this form is mandatory)

APRN23

Last Name_____ First Name_____MI_____

State _____ License # _____ Expiration Date_____ _____

To receive continuing education credit, completion of this Evaluation is mandatory.
Please answer all of the following questions and provide your signature at the bottom of this page.
Your postmark or facsimile date will be used as your completion date.

Please read the following questions and choose the most appropriate answer for each course completed.

1. Was the course content new or review?
2. How much time did you spend on this activity?
3. Would you recommend this course to your peers?
4. Did the course content support the stated course objective?
5. Did the course content demonstrate the author's knowledge of the subject?
6. Was the course content free of bias?
7. Before completing the course, did you identify the necessity for education on the topic to improve your nursing practice?
8. Have you achieved all of the stated learning objectives of this course?
9. Has what you think or feel about this topic changed?
10. Did study questions throughout the course promote recall of learning objectives?
11. Did evidence-based practice recommendations assist in determining the validity or relevance of the information?
12. Are you more confident in your ability to provide nursing care after completing this course?
13. Do you plan to make changes in your nursing practice as a result of this course content?

#95500 Opioid Safety 5 Contact Hours	**#96790** Psychedelic Medicine 10 Contact Hours	**#30993** Acute Coronary Syndrome 15 Contact Hours
1. ☐ New ☐ Review	1. ☐ New ☐ Review	1. ☐ New ☐ Review
2. _____ Hours	2. _____ Hours	2. _____ Hours
3. ☐ Yes ☐ No	3. ☐ Yes ☐ No	3. ☐ Yes ☐ No
4. ☐ Yes ☐ No	4. ☐ Yes ☐ No	4. ☐ Yes ☐ No
5. ☐ Yes ☐ No	5. ☐ Yes ☐ No	5. ☐ Yes ☐ No
6. ☐ Yes ☐ No	6. ☐ Yes ☐ No	6. ☐ Yes ☐ No
7. ☐ Yes ☐ No	7. ☐ Yes ☐ No	7. ☐ Yes ☐ No
8. ☐ Yes ☐ No	8. ☐ Yes ☐ No	8. ☐ Yes ☐ No
9. ☐ Yes ☐ No	9. ☐ Yes ☐ No	9. ☐ Yes ☐ No
10. ☐ Yes ☐ No	10. ☐ Yes ☐ No	10. ☐ Yes ☐ No
11. ☐ Yes ☐ No	11. ☐ Yes ☐ No	11. ☐ Yes ☐ No
12. ☐ Yes ☐ No	12. ☐ Yes ☐ No	12. ☐ Yes ☐ No
13. ☐ Yes ☐ No	13. ☐ Yes ☐ No	13. ☐ Yes ☐ No

#95500 Opioid Safety: Balancing Benefits and Risks — If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team?_____
_____

#96790 Psychedelic Medicine and Interventional Psychiatry — If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team?_____
_____

#30993 Acute Coronary Syndrome — If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team? _____
_____

May we contact you later regarding your comments about these activities? ☐ Yes ☐ No

I have read the course(s) and completed the Evaluation(s) in full.
I understand my postmark or facsimile date will be used as my completion date.

Signature_____

Signature required to receive continuing education credit.

Want More CE Choices?

Get One Year of **Unlimited Online APRN CE** starting at only $125!

Includes access to our entire course library of more than 1,500 hours, including over 500 pharmacology hours, special offers, and state-required courses!

The following Online Specials are included with your Online Unlimited Subscription or may be purchased individually.

NATURAL MEDICINE SPECIAL OFFER
Cannabinoids • Top-Selling Supplements • Commonly Abused Supplements • Acupuncture • Microbiome Medley • Glucosamine and Chondroitin • The Scoop on Collagen
17.5 Hours $49

GERIATRIC SPECIAL OFFER
Aging and Long-Term Care • Osteoporosis • Alzheimer Disease
23 Hours $52

TRAUMA SPECIAL OFFER
Postoperative Complications • Transport Methods for the Critically Ill Patient
30 Hours $62

DESIGN A DEAL SPECIAL OFFER
Choose from our entire library of courses to create your own unique Special Offer.
$52 to $73 (Based on number of hours selected)
NetCE.com/Design

ADVANCED PRACTICE SPECIAL OFFER
Bacterial Sexually Transmitted Infections • Diagnosing and Managing Headaches • Autoimmune Diseases
30 Hours (includes 22 Pharm Hours) $73

PHARMACOLOGY SPECIAL OFFER
Epidural Analgesia Update • Diabetes Pharmacology • Moderate Sedation/Analgesia
30 Hours (includes 28 Pharm Hours) $73

For more details, go to NetCE.com/APRNUnlimited

BUSINESS HOURS: Monday through Friday, 8am-5pm Pacific Time. We are closed on weekends and holidays.

CUSTOMER SERVICE: 800-232-4238 or help@netce.com. Call or email us for customer assistance, course catalogs, additional certificates, or transcripts. If you require special assistance, please contact the Director of Development and Academic Affairs to inform her of your needs by calling 800-232-4238.

RETURN POLICY: Satisfaction guaranteed or your money back within 30 days of purchase, unless certificates have been issued. Please return the materials and include a brief note of explanation. For more information, please contact help@NetCE.com.

TURNAROUND TIME: If sent by mail, your order is processed within 2 to 3 weeks from the day it was received. **For the fastest processing time, visit www.NetCE.com to purchase, complete for credit, and receive your certificates instantly.**

MAILING PREFERENCES: To modify your mailing preferences or to view our privacy policy, please go to www.NetCE.com.

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

RETURNED CHECKS: If, for any reason, your check is returned, you will be contacted requesting a cashier's check or money order for the full amount of the order plus a $35 reinstatement fee. In addition, we are unable to accept temporary checks.

If you have questions about your license or certification renewal or state requirements, please contact your board. A list of approvals and accreditations is available on our website at www.NetCE.com.

NetCE
a trchealthcare brand

NetCE | P.O. Box 997571 | Sacramento, CA 95899 | 800-232-4238 | Fax: 916-783-6067

NetCE
a trchealthcare brand

PRESORTED
STANDARD
U.S. POSTAGE PAID
PERMIT NO. 182
SACRAMENTO, CA

P.O. Box 997571
Sacramento, CA 95899

Vol. 148
No. 17
NYAPRN23

Complete online at NetCE.com/APRN23

Quick Code#

Customer ID#

Scan this QR code to get started.
If you do not have a smartphone or
QR code reader, please visit
NetCE.com/APRN23.

Like us at **NetCEContinuingEducation**

We Recycle